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Application Number	Herewith
Filing Date	Concurrently Herewith
First Named Inventor	Steven C. Quay
Title	METHODS FOR MAKING AND USING ENDOXIFEN
Art Unit	Not Applicable
Examiner Name	Not Applicable
Attorney Docket Number	438558-758053

SIGNATURE of Applicant or Patent Practitioner

Signature	/Erin M. Gaffney/	Date (Optional)	2023-03-30
Name	Erin M. Gaffney, Ph.D.	Registration Number	81,479
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

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I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Atossa Therapeutics, Inc.

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☑ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature	/Kyle Guse/	Date (Optional)	5/25/22
Name	Kyle Guse		
Title	Chief Financial Officer and General Counsel		

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Electronic Acknowledgement Receipt

EFS ID:	47765261
Application Number:	18128536
International Application Number:	
Confirmation Number:	1025
Title of Invention:	METHODS FOR MAKING AND USING ENDOXIFEN
First Named Inventor/Applicant Name:	Steven C. Quay
Customer Number:	187495
Filer:	Erin Gaffney/Christina Campbell
Filer Authorized By:	Erin Gaffney
Attorney Docket Number:	438558-758053
Receipt Date:	30-MAR-2023
Filing Date:	
Time Stamp:	13:48:00
Application Type:	Utility under 35 USC 111(a)

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		438558-758053-application.pdf	1071971 048bceccf366b87ebe025a3a77153c523c9253b4	yes	137

	Multipart Description/PDF files in .zip description				
	Document Description	**Start**	**End**		
	Specification	1	117		
	Claims	118	136		
	Abstract	137	137		
Warnings:					
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2	Application Data Sheet	438558-758053-ads.pdf	2281707 4ba84c1ca9edf0bddd7f91b2309573ad38069ba5	no	10
Warnings:					
Information:					
3	Drawings-only black and white line drawings	438558-758053-drawings.pdf	2260133 83b3091dde5e65014cc0ef387a9956b9249ca06f	no	13
Warnings:					
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4	Oath or Declaration filed	438558-758053-decs.pdf	517495 b561154cb40bd7a1c5401518d7a8194f180df1fa	no	5
Warnings:					
Information:					
5	Power of Attorney	438558-758053-poa.pdf	294086 2c84501524c74bbf27d8da1c1b69101be9ff155f	no	2
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New International Application Filed with the USPTO as a Receiving Office

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Docket No. 438558-758053 (758USC3)

PATENT APPLICATION

METHODS FOR MAKING AND USING ENDOXIFEN

Inventors: Steven C. Quay,
Citizen of the United States, Residing in
Seattle, Washington

Yao-Lin Sun,
Citizen of Taiwan, Residing in
Tainan City, Taiwan

LungHu Wang,
Citizen of Taiwan, Residing in
Kaohsiung City, Taiwan

ChangJung Wu,
Citizen of Taiwan, Residing in
Kaohsiung City, Taiwan

ChuanDer Huang,
Citizen of Taiwan, Residing in
Tainan City, Taiwan

Assignee: Atossa Therapeutics, Inc.
107 Spring Street
Seattle, Washington 98104

Entity: Small business concern



701 5th Avenue, Suite 6900
Seattle, WA 98104
(206) 839-4800
Facsimile: (206) 839-4801 Fax
us.dlapiper.com

Filed Electronically on: March 30, 2023

METHODS FOR MAKING AND USING ENDOXIFEN

CROSS-REFERENCE

[0001] This application is a continuation of U.S. Patent Application No. 18/090,757, filed December 29, 2022, which is a continuation of U.S. Application No. 17/580,428, filed January 20, 2022, now U.S. Patent No. 11,572,334, which is a continuation of U.S. Patent Application No. 16/641,985, filed February 25, 2020, now U.S. Patent No. 11,261,151, which is a U.S. National Phase Application under 35 U.S.C. § 371 of International Application No. PCT/US2018/050272, filed September 10, 2018, which claims the benefit of U.S. Provisional Application No. 62/556,799, filed September 11, 2017; U.S. Provisional Application No. 62/556,884, filed September 11, 2017; U.S. Provisional Application No. 62/624,787, filed January 31, 2018; and U.S. Provisional Application No. 62/693,885, filed July 3, 2018, each incorporated herein by reference in their entireties.

BACKGROUND OF THE INVENTION

[0002] Breast cancer is by far the most common form of cancer in women, and it is the second leading cause of cancer death in humans. Despite advances in diagnosing and treating breast cancer, the prevalence of this disease has been steadily rising at a rate of about 1% per year since 1940. Today, the likelihood that a woman living in North America will develop breast cancer during her lifetime is one in eight. In addition to breast cancers, other breast disorders affecting a large number of women include benign but often precancerous lesions, such as ductal hyperplasia, lobular hyperplasia, atypical ductal hyperplasia, and atypical lobular hyperplasia.

[0003] Current best practice for the treatment of breast cancer is to diagnose breast cancer with mammography and then treat the patient with surgery, radiation therapy, and chemotherapy. The current widespread use of mammography has resulted in improved detection of breast cancer. Although breast cancer is about 100 times less common among men than among women, the lifetime risk of men getting breast cancer is about 1 in 1,000. About 2,470 new cases of invasive breast cancer will be diagnosed in men and about 460 men will die from breast cancer. American Cancer Society estimates that in 2017, 255,180 new cases of breast cancer will be diagnosed in both men and women combined and 41,070 subjects will die of breast cancer. Nonetheless, the death rate due to breast cancer has remained relatively unchanged at about 21 deaths per 100,000 women and 0.4 deaths per 100,000 men. All too often, breast cancer is discovered at a stage that is too far advanced, when therapeutic options and survival rates are severely limited.

[0004] Breast cancers include any malignant tumor of breast cells. There are several types of breast cancer. Exemplary breast cancers include, but are not limited to, ductal carcinoma in situ, lobular

carcinoma in situ, invasive (or infiltrating) ductal carcinoma, invasive (or infiltrating) lobular carcinoma, inflammatory breast cancer, triple-negative breast cancer, ER+ breast cancer, HER2+ breast cancer, adenoid cystic (or adenocystic) carcinoma, low-grade adenosquamous carcinoma, medullary carcinoma, mucinous (or colloid) carcinoma, papillary carcinoma, tubular carcinoma, metaplastic carcinoma, and micropapillary carcinoma. A single breast tumor can be a combination of these types or be a mixture of invasive and in situ cancer.

[0005] Tamoxifen is a selective estrogen receptor modulator that is used for the treatment of women with endocrine responsive breast cancer, i.e., hormone-dependent or hormone-sensitive breast cancer. Adjuvant therapy primarily via oral delivery of tamoxifen is known to have severe side effects such as vasomotor symptoms, for example hot flashes, and reproductive tract (gynecologic) cancers. Patient compliance remains a problem with tamoxifen therapy. Further, the majority of the individuals on adjuvant tamoxifen therapy do not respond to the drug and 30 – 50% of the patients subsequently die of their disease.

[0006] Several cytochrome P450 (CYP) mutations have been proposed to cause reduced conversion of tamoxifen to its active metabolite, endoxifen, and reduce tamoxifen efficacy and increase resistance to the drug (Dickschen et al. Front Pharmacol. 2012; 3: 92. PMCID: PMC3357105). So far, over 140 allelic variants of CYP2D6 have been described and a substantial part of these are associated with reduced or absent activity of the encoded enzyme. Based on the combination of the carried alleles, each individual subject can be classified into one of four phenotypic groups: poor metabolizer (PM) with plasma endoxifen levels less than 30 nM, intermediate metabolizer (IM), extensive metabolizer (EM) and ultra-rapid metabolizer (UM), reflecting variations in levels of serum endoxifen. However, changes in the CYP genotype do not fully explain the tamoxifen resistance and the reduced endoxifen levels observed in some subjects.

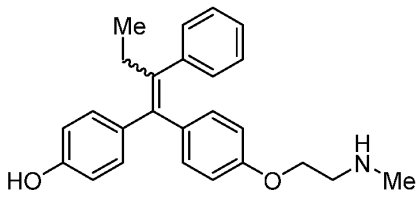
[0007] Therefore, several alternatives to tamoxifen are being developed for the treatment of breast cancer, which include low dose-tamoxifen (Lazzeroni M et al. Breast Cancer Res. 2012 Oct 29;14(5):214) and tamoxifen's active metabolites, afimoxifene (*see*, U.S. Patent Nos. 7,485,623; 7,507,769; 7,704,516; 7,786,172; 7,968,532; and 8,048,927; Mansel R et al. Breast Cancer Res Treat. 2007 Dec;106(3):389-97. PubMed PMID: 17351746; Rouanet P et al. J ClinOncol. 2005 May 1;23(13):2980-7. PubMed PMID: 15860853), endoxifen (*see*, US9333190; U.S. Patent Nos. 9,220,680; 9,090,640; and 9,200,045; U.S. Publication Nos. 2009/0291134 and US20100112041), and their derivatives (*see*, U.S. Patent Nos. 8,063,249; U.S. Publication Nos. 2015/0080339 and 2014/0193334). It is widely accepted that (Z)-endoxifen is the main active metabolite responsible for the clinical efficacy of tamoxifen.

[0008] While hydrochloride and citrate salts of endoxifen (*See*, *e.g.*, Fauq *et al.*, Bioorganic & Medicinal Chemistry Letters. 20 (2010) 3036 – 3038; Stearns *et al.*, J. Natl. Cancer Inst. Vol 95, No. 23, 2003; US Publication Nos. 2009/0291134 and 2010/0112041; Clinical Trials Gov. Identifier Nos. NCT01273168 and NCT02311933; Goetz et al., 2015, San Antonio Cancer Symposium; Ahmad *et al.*, Clinical Pharmacology & Therapeutics. 88(6) 814-817, 2010; and J Clin. Oncol. 30, 2012 (suppl; abstr 3089); Ahmad et al. Breast Cancer Research and Treatment 2010, 122, 579-584) are known in the art and currently under evaluation for metastatic cancer, there remains unmet medical need for new compositions and methods for the treatment and/or prevention of hormone-dependent breast and reproductive tract (gynecologic) disorders.

SUMMARY OF THE INVENTION

[0009] The present disclosure addresses this need by providing compositions and methods for the treatment and/or prevention of hormone-dependent breast and reproductive tract (gynecologic) disorders. In certain aspects, the present disclosure provides novel industrially scalable methods of making Z-endoxifen or salts thereof, crystalline forms of endoxifen, and compositions comprising them. In certain aspects, the present disclosure provides novel crystalline forms of endoxifen wich may provide advantages including improved bioavailability and stability relative to other crystalline or amorphous forms.

[0010] In certain aspects, the present disclosure provides a composition comprising a crystalline form of a compound of Formula (III):



Formula (III).

[0011] In some embodiments, at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer. In some embodiments, the crystalline form is Form I of the compound of Formula (III). Crystalline Form I may be characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, and optionally further comprising at least one peak selected from 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3° two theta. In some embodiments, the x-ray powder diffraction pattern further comprises at least one peak selected from 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta. The x-ray powder diffraction pattern may further comprise peaks at 12.3 ± 0.3°, 16.0 ± 0.3°, 18.8 ± 0.3°, 26.5 ± 0.3°, 28.0 ± 0.3°

and 29.0 ± 0.3° two theta. In some embodiments, crystalline Form I is characterized by an x-ray powder diffraction pattern substantially as set forth in **Fig. 9** or **Fig. 10**. Greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition may be crystalline Form I. In some embodiments, the composition comprises 0.01 mg to 200 mg of crystalline Form I, such as about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form I.

[0012] In some embodiments, the composition comprises the (E)-isomer and the (Z)-isomer of the compound of Formula (III) in an E/Z ratio between 0.9 and 1.3, such as about 1.1. In some embodiments, the crystalline form is Form II of the compound of Formula (III). Crystalline Form II may be characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta, and optionally further comprising a peak at 22.0 ± 0.3° two theta. In some embodiments, the x-ray powder diffraction pattern further comprises at least one peak selected from 6.6 ± 0.3°, 13.3 ± 0.3° and 20.0 ± 0.3° two theta. The x-ray powder diffraction pattern may further comprise peaks at 6.6 ± 0.3°, 13.3 ± 0.3°, 20.0 ± 0.3° and 22.0 ± 0.3° two theta. In some embodiments, crystalline Form II is characterized by an x-ray powder diffraction pattern substantially as set forth in **Fig. 11** or **Fig. 12**. Greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition may be crystalline Form II. In some embodiments, the composition comprises 0.01 mg to 200 mg of crystalline Form II, such as about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form II.

[0013] In some embodiments, the composition comprises the (E)-isomer and the (Z)-isomer of the compound of Formula (III) in an E/Z ratio between 0.9 and 1.3, such as about 1.1. In some embodiments, the crystalline form is Form III of the compound of Formula (III). Crystalline Form III may be characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta, and optionally further comprising a peak at 25.3 ± 0.3° two theta. In some embodiments, the x-ray powder diffraction pattern further comprises at least one peak selected from 18.2 ± 0.3°, 22.5 ± 0.3° and 26.8 ± 0.3° two theta. The x-ray powder diffraction pattern may further comprise peaks at 18.2 ± 0.3°, 22.5 ± 0.3°, 25.3 ± 0.3° and 26.8 ± 0.3° two theta. In some embodiments, crystalline Form III is characterized by an x-ray powder diffraction pattern substantially as set forth in **Fig. 13**. Greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition may be crystalline Form III. In some embodiments, the composition comprises 0.01 mg to 200 mg of crystalline Form III, such as about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form III.

[0014] In certain aspects, the present disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the composition comprising a crystalline form

of a compound of Formula (III). A composition of the present disclosure may be formulated for oral, parenteral, topical, or intraductal delivery. In some embodiments, the composition is formulated for oral delivery as a tablet, a caplet, a capsule, or a pill. In some embodiments, a mean half-life of endoxifen in a subject treated with the composition is between 30 hours to 60 hours. A composition comprising a crystalline form of a compound of Formula (III) may be formulated for oral delivery as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule. In some embodiments, the composition is administered to a subject for the treatment or prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in the subject.

[0015] In certain aspects, the present disclosure provides an oral composition comprising 1 mg to 200 mg per unit dose of the composition comprising a crystalline form of a compound of Formula (III) for administration to a subject in need thereof, wherein daily administration of the oral composition achieves in the subject:

a steady state plasma level of endoxifen within 7 to 21 days;

a steady state plasma level of endoxifen ranging from 25 nM to 300 nM;

a steady state plasma level of endoxifen greater than 30 nM;

maximal plasma levels of endoxifen within 2 to 10 hours after administering; or

any combination thereof.

[0016] In some embodiments, a mean half-life of endoxifen in a subject treated with the composition comprising a crystalline form of a compound of Formula (III) is between 40 hours to 55 hours. In some embodiments, the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule. In some embodiments, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of endoxifen in the composition is released in the intestines. In some embodiments, the composition comprising a crystalline form of a compound of Formula (III) exhibits a mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of endoxifen of 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL.

[0017] In certain aspects, the present disclosure provides a method of treating a subject in need thereof, the method comprising administering to the subject the composition comprising a crystalline form of a compound of Formula (III). In some embodiments, the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both. The hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder

may be a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer. In some embodiments, the subject has prostate cancer and has or is at risk of having gynecomastia. The subject may have tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder. In some embodiments, the subject is or will be treated with an SSRI drug selected from the group consisting of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone.

[0018] In practicing any of the subject methods, the composition may comprise 0.01 mg to 200 mg of (Z)-endoxifen. In some embodiments, the subject is administered about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen daily. In some embodiments, a steady state plasma level of endoxifen in the subject is greater than 30 nM. The steady state plasma level of endoxifen may be achieved within 7 to 21 days of the first administration of the composition. In some embodiments, time to maximum plasma levels of endoxifen ranges from 2 hours to 10 hours or from 4 hours to 8 hours after administering the composition.

[0019] In certain aspects, the present disclosure provides a method of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, the method comprising administering the composition comprising a crystalline form of a compound of Formula (III), wherein administration of the composition achieves:

a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;

a time to maximum plasma levels of endoxifen ranging from 4 hours to 8 hours after administration; and

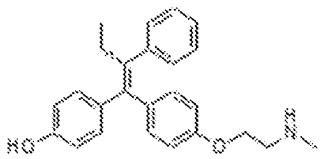
a steady state plasma level of endoxifen greater than 30 nM.

[0020] In some embodiments, the hormone-dependent breast disorder and the hormone-dependent reproductive tract disorder are selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer.

[0021] In practicing any of the subject methods, the composition may comprise 0.01 mg to 200 mg of (Z)-endoxifen. In some embodiments, the subject is administered about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen. The mean area under the curve extrapolated to time infinity

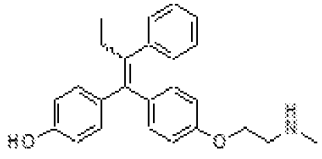
($AUC_{0\text{-}inf}$) of endoxifen may be 200 hr*ng/mL to 10000 hr*ng/mL, 300 hr*ng/mL to 8000 hr*ng/mL, 400 hr*ng/mL to 6000 hr*ng/mL or 700 hr*ng/mL to 6000 hr*ng/mL. In some embodiments, the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule. In some embodiments, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of endoxifen in the composition is released in the intestines. The composition may be administered once a day, twice a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually.

[0022] In one aspect, the present disclosure provides an industrially scalable process for manufacturing (Z)-endoxifen or salts thereof, comprising the steps of: (a) subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), represented by



to fractional crystallization from a first solvent to form a first crystalline solid and first crystalline mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen; (b) subjecting the first mother liquor to recrystallization from a second solvent by concentrating the first mother liquor or by swapping out the first solvent from the first mother liquor one or more times with the second solvent, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥90% (Z)-endoxifen; and (c) optionally, subjecting the second crystalline solid to recrystallization from a third solvent or chromatographic treatment one or more times to form a third crystalline solid. In some embodiments, any one or more of the first solvent, the second solvent, and the third solvent are preheated to a temperature ranging from 40 °C to 80 °C.

[0023] In some aspects, the present disclosure provides an industrially scalable process for manufacturing crystalline Form I of the compound of Formula (III), comprising the steps of (a) subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), represented by

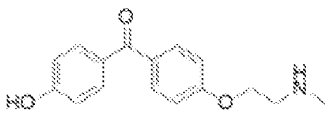


to fractional crystallization from a first solvent to form a first crystalline solid and first mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen; (b) subjecting the first mother liquor to recrystallization from a second solvent by concentrating the first mother liquor or by swapping out the first solvent from the first mother liquor with the second solvent one or more times, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥ 90% (Z)-endoxifen; and (c) subjecting the second crystalline solid to recrystallization from a third solvent or chromatographic treatment one or more times to form a third crystalline solid, wherein the third crystalline solid is crystalline Form I of the compound of Formula (III).

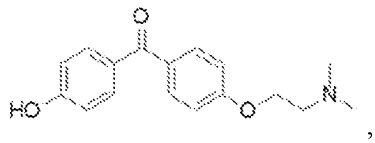
[0024] In certain aspects, the present dislcosure provides a crystalline form of a compound of Formula (III) produced according to a method described herein. In some embodiments, the crystalline form is Form I of the compound of Formula (III). In some embodiments, the crystalline form is Form II of the compound of Formula (III). In some embodiments, the crystalline form is Form III of the compound of Formula (III).

[0025] In another aspect, the present disclosure provides that the mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), in step a is pretreated with 6N HCl and neutralized with 8N NaOH.

[0026] In another aspect, the industrially scalable process further comprises preparing the mixture of (E)-endoxifen and (Z)-endoxifen by coupling the compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, to propiophenone mediated by a McMurry reaction via a titanium salt and a reducing agent in an inert organic solvent to form the mixture of (E)-endoxifen and (Z)-endoxifen; and wherein the compound of Formula (II) has a structure represented by

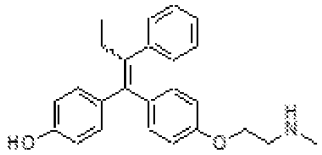


[0027] In yet another aspect, the industrially scalable process further comprises preparing the compound of Formula (II) by demethylating [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone, the compound of Formula (I), wherein the compound of Formula (I) has the structure



with a demethylating agent and a proton acceptor in an inert organic solvent to form the compound of Formula (II).

[0028] The present disclosure also provides an industrially scalable process for manufacturing (Z)-endoxifen and salts thereof, comprising the steps of: (a) subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III) represented by



to fractional crystallization from ethyl acetate to form a first crystalline solid and first crystalline mother liquor, wherein the first mother liquor has an E/Z ratio of at least 30% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen; (b) subjecting the first mother liquor to recrystallization from IPA or IPA/PPW (1:1 v/v) by concentrating the first mother liquor, or by swapping out ethyl acetate from the first mother liquor one or more times with IPA or IPA/PPW, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥90% (Z)-endoxifen; and (b) optionally, subjecting the second crystalline solid to recrystallization from ethanol or column chromatographic treatment one or more times to form a third crystalline solid.

[0029] In some embodiments, the mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), is prepared by coupling the compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, to propiophenone mediated by a McMurry reaction comprising the steps of: (a) reacting the compound of Formula (II) with propiophenone (1:0.01 to 1.5 wt/wt) in an inert organic solvent (1:1 to 1: 20 wt/wt); (b) preparing a titanium salt (1:0.1 to 1:12 wt/wt) and a reducing agent (1:0.01 to 1:10 wt/wt) in an inert organic solvent (1:1 to 1: 20 wt/wt); and (c) reacting the compound of Formula (II) of step (a) with the titanium salt and a reducing agent in an inert organic solvent of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen; and wherein wt/wt is with respect to the compound of Formula (II).

[0030] In other embodiments, the mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), is prepared by coupling the compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, to propiophenone mediated by a McMurry reaction comprising the steps of: (a) reacting the compound of Formula (II) with propiophenone (1:0.01 to 1:5 wt/wt) in THF (1:1 to 1:20 wt/wt); (b) preparing a $TiCl_4$ (0.1 to 4 wt/wt) and Zn (0.01 to 1:2 wt./wt) in THF (1:1 to 1:20 wt/wt; and (c) reacting the compound of Formula (II) of step (a) with the $TiCl_4$ and Zn in THF of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen; and wherein wt/wt is with respect to the compound of Formula (II).

[0031] In some embodiments, the compound of Formula (II) is generated by demethylating the compound of Formula (I) with a demethylating agent (1:0.5 to 1:10 wt/wt) and a proton acceptor (1:0.5 to 1:10 wt/wt) in an inert organic solvent (1:1 to 1: 20 wt/wt) to form a compound of Formula (II), wherein the wt/wt is with respect to the compound of Formula (I).

[0032] In some embodiments, the compound of Formula (II) is prepared by demethylating the compound of Formula (I) with 1-chloroethyl chloroformate and DIPEA in THF to form the compound of Formula (II) comprising the steps of: (a) reacting the compound of Formula (I) with DIPEA (1:0.5 to 1:10 wt/wt) in THF (1:20 wt/wt); (b) adding 1-chloroethyl chloroformate (1:0.5 to 1:10 wt./wt); (c) distilling with methanol one or more times (1:1 to 1:10 wt./wt); (e) reacting with methanol (1:1 to 1:5 wt/wt)/HCl (1:1 to 1:10 wt/wt); and (e) neutralizing with NaOH (1:1 to 1:10 wt/wt); and wherein wt/wt is with respect to the compound of Formula (I).

[0033] In another aspect, the present disclosure provides process for making (Z)-endoxifen gluconate salts by reacting (Z)-endoxifen with D-gluconate or L-Gluconate to form (Z)-endoxifen L-gluconate or (Z)-endoxifen D-gluconate.

[0034] In still another aspect, the present disclosure provides that (Z)-endoxifen, (E)-endoxifen, compounds of Formula (III), the compound of Formula (II), and salts thereof prepared by any of the processes as described herein are stable. In a particular aspect, the (Z)-endoxifen free base is stable at ambient temperature for at least 9 months.

[0035] In certain aspects, the present disclosure provides an industrially scalable process for manufacturing crystalline Form II or III of the compound of Formula (III), comprising (a) reacting to 6N HCL (1:1 to 1:5 wt/wt) in ethyl acetate (1:1 to 1:20 wt/wt) a starting mixture of (E)-endoxifen and (Z)-endoxifen having an E/Z-ratio ranging from 99:1 to 40:60; (b) neutralizing with 8N NaOH (1:1 to 1:20 wt/wt); (c) washing one or more times with ethyl acetate; (d) washing one or more times with a mixture of ethyl acetate and n-heptane; and (e) recovering crystalline Form II or III of the

compound of Formula (III); wherein wt/wt is with respect the starting mixture of (E)-endoxifen and (Z)-endoxifen.

[0036] In yet another aspect, the present disclosure provides a composition comprising (Z)-endoxifen free base or a salt thereof prepared according to any of the processes described herein. The compositions are formulated for oral, parenteral, topical, and intraductal delivery. The compositions are formulated for oral delivery as tablets, caplets, capsules, or pills. In some embodiments, the compositions are formulated for oral delivery tablet as enteric tablets, enteric caplets, enteric capsules, delayed-release tablets, delayed-release caplets, and delayed-release capsules.

[0037] In certain aspects, the present disclosure provides compositions having certain pharmacokinetic profiles. In one aspect, the present disclosure provides that at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% of the endoxifen in the compositions is released in intestines. In another aspect, the present disclosure provides that the endoxifen in the compositions has a mean half-life of in a subject ranging from 30 hours to 60 hours after administration. In some embodiments, the mean half-life of endoxifen in a subject ranges from 40 hours to 55 hours after administration. In another aspect, the present disclosure provides that the mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL.

[0038] In another aspect, the present disclosure provides oral compositions comprising 1 mg to 200 mg per unit dose of (Z)-endoxifen free base or a salt thereof, for administration to a subject in need thereof, wherein daily administration of the oral composition achieves in the subject: (i) a steady state plasma level of endoxifen within 7 to 21 days; or (ii) a steady state plasma level of endoxifen ranging from 25 nM to 300 nM; or (iii) a steady state plasma level of endoxifen greater than 30 nM; or (iv) maximal plasma levels of endoxifen within 2 to 10 hours after administering; or (v) any combination thereof. The present disclosure also provides that the compositions are administered to a subject in need thereof for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in a subject.

[0039] In certain aspect, the present disclosure provides methods of treating a subject in need thereof, the method comprising administering to the subject an oral composition as disclosed herein. In some embodiments, the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both. In various embodiments, the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast

disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

[0040] In some embodiments, the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

[0041] In certain aspects, the present disclosure provides certain patient populations that would benefit from such methods of treatment. In some embodiments, the patient population is a tamoxifen-refractory or tamoxifen resistant population. In certain embodiments, the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder. In other embodiments, the patient population comprises subjects that are or will be treated with an SSRI drug selected from the group consisting of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone.

[0042] In an aspect, the present disclosure provides certain doses of (Z)-endoxifen to be administered to subjects in need thereof. In various embodiments, the subjects are administered 0.01 mg to 200 mg of (Z)-endoxifen. In certain embodiments, the subject is administered 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen daily.

[0043] In another aspect, the present disclosure provides methods of treatment of subjects, wherein a steady state plasma level of endoxifen in of the subject is greater than 30 nM upon administration of the compositions. In some embodiments, such a steady state plasma level of endoxifen is achieved within 7 to 21 days of the first administration of the composition. In some embodiments, the time to maximum plasma levels of endoxifen ranges from 2 hours to 10 hours or from 4 hours to 8 hours after administering the composition.

[0044] In another aspect, the present disclosure provides methods of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, the method comprising administering an oral composition comprising (Z)-endoxifen or a salt thereof, wherein administration of the composition achieves: (i) a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration; (ii) a time to maximum plasma levels of endoxifen ranging from 4 hours to 8 hours after administration; and (iii) a steady state plasma level of endoxifen greater than 30 nM. In certain embodiments, the subject is administered 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen. In other embodiments, the mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700

hr*ng/mL to 6000 hr*ng/mL. In some embodiments, the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule. In some embodiments, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90% of the endoxifen is released in intestines. In some embodiments, the composition is administered once a day, twice a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually. In some embodiments, the hormone-dependent breast disorder and the hormone-dependent reproductive tract disorder are selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer.

INCORPORATION BY REFERENCE

[0045] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

BRIEF DESCRIPTION OF THE DRAWINGS

[0046] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0047] **Fig. 1** is a scheme depicting the metabolic route of tamoxifen to endoxifen and other metabolites. The plasma concentrations of 4-hydroxytamoxifen are low relative to those of N-desmethyl tamoxifen, indicating that the primary route for metabolism of the parent drug is via N-demethylation by cytochrome P450 3A4 (CYP3A4) to N-desmethyl tamoxifen, followed by hydroxylation by cytochrome P450 2D6 (CYP2D6) to endoxifen.

[0048] **Fig. 2** is a representative infrared spectrum of (Z)-endoxifen free base prepared using methods disclosed herein.

[0049] **Fig. 3** shows the time to maximum serum levels (nM) of endoxifen following treatment with placebo or 1 mg, 2 mg or 4 mg endoxifen capsules.

[0050] Fig. 4 shows the time to maximum serum levels of endoxifen following treatment with placebo or 1 mg, 2 mg or 4 mg endoxifen capsules at day 1 and day 21. The time post-dose (hours) is plotted on the X-axis and mean serum concentration (ng/mL) is plotted on the Y-axis.

[0051] Fig. 5 shows the time to achieve steady state serum levels of endoxifen following treatment with placebo or 1 mg, 2 mg or 4 mg endoxifen capsules from day 0 (day 0 refers to day 8 on the X-axis) to day 21. The X-axis is time in days (Day 8 to Day 21) and the Y-axis is mean serum concentration in ng/mL. Blood was drawn on each day from day 0 to the end of the clinical trial period. Subjects were dosed on day 1 and plasma endoxifen levels were measured as shown in **Table 17**. Subjects were subsequently dosed daily starting on day 8 (labeled day 8 in **Fig. 5**) until the end of study period.

[0052] Fig. 6 shows mean serum concentrations (ng/mL) over time following treatment with placebo or 1 mg, 2 mg or 4 mg endoxifen capsules at day 1 and day 21 (Linear).

[0053] Fig. 7 shows mean serum concentrations (ng/mL) over time following treatment with placebo or 1 mg, 2 mg or 4 mg endoxifen capsules at day 1 and day 21 (Semi-log).

[0054] Fig. 8 shows mean serum concentrations (nM) over time following treatment with placebo or 1 mg, 2 mg or 4 mg endoxifen capsules at day 1 and day 21 (Linear).

[0055] Fig. 9 is an XRPD pattern obtained from a sample of Form I of the compound of Formula (III).

[0056] Fig. 10 is an XRPD pattern obtained from a sample of Form I of the compound of Formula (III).

[0057] Fig. 11 is an XRPD pattern obtained from a sample of Form II of the compound of Formula (III).

[0058] Fig. 12 is an XRPD pattern obtained from a sample of Form II of the compound of Formula (III).

[0059] Fig. 13 is an XRPD pattern obtained from a sample of Form III of the compound of Formula (III).

DETAILED DESCRIPTION OF THE INVENTION

[0060] Compounds are described using standard nomenclature. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs.

[0061] As used herein, the terms "a," "an," and "the" include plural reference unless the context dictates otherwise.

[0062] As used herein, the terms "active pharmaceutical ingredient", "active ingredient", "API," "drug," "active," "actives" or "therapeutic agent" may be used interchangeably to refer to the pharmaceutically active compound(s) in a pharmaceutical composition. This is in contrast to other ingredients in the compositions, such as excipients, which are substantially or completely pharmaceutically inert. A suitable API in accordance with the present disclosure is one where there is or likely may be patient compliance issues for treating a certain disease, condition, or disorder. The therapeutic agent as used herein includes the active compound and its salts, prodrugs, and metabolites. As used herein the term "drug" means a compound intended for use in diagnosis, cure, mitigation, treatment, and/or prevention of disease in man or other animals.

[0063] As used herein, "adjuvant therapy" refers to a therapy that follows a primary therapy and that is administered to subjects at risk of relapsing. Adjuvant systemic therapy in case of breast cancer or reproductive tract cancer, for example with tamoxifen, usually begins soon after primary therapy to delay recurrence, prolong survival or cure a subject.

[0064] As used herein, the term "tamoxifen" refers to (Z)-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-N,N-dimethylethanamine. Tamoxifen can also refer to the E-isomer or a combination of the E-isomer and the Z-isomer.

[0065] As used herein, the terms "4-hydroxytamoxifen," "afimoxifene," and "4-OHT" used interchangeably refer to 4-1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-phenylbut-1-enyl]phenol, and constitutes an active metabolite of tamoxifen. 4-OHT can refer to the Z-isomer, E-isomer or a combination thereof.

[0066] As used herein, the term "endoxifen" refers to 4-hydroxy-N-desmethyl-tamoxifen. It is a secondary active metabolite of tamoxifen.

[0067] Embodiments that reference throughout this specification to "a compound", such as compounds of Formula (I), Formula (II), Formula (III) and Formula (IV), include the polymorphic, salt, free base, co-crystal, and solvate forms of the formulas and/or compounds disclosed herein. Thus, the appearances of the phrases "a compound", "compound of Formula (I)", "compound of Formula (II)", "compounds of Formula (III)" and "compound of Formula (IV)" include Form I of the compound of Formula (IV), Forms II-III of the compounds of Formula (III), the free base of the compound of Formula (IV), the free base of the compounds of Formula (III), and/or the gluconate salts as described herein.

[0068] The terms "crystalline form", "polymorph" and "Form" may be used interchangeably herein, and are meant to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, salts, solvates, hydrates, unsolvated polymorphs

(including anhydrates), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to. Compound of the present disclosure include crystalline and amorphous forms of those compounds, including, for example, polymorphs, pseudopolymorphs, salts, solvates, hydrates, unsolvated polymorphs (including anhydrates), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof.

[0069] All compounds disclosed herein are further understood to include all possible isotopes of atoms occurring in the compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of example, and without limitation, isotopes of hydrogen include tritium and deuterium and isotopes of carbon include ^{11}C, ^{13}C and ^{14}C.

[0070] As used herein and in the claims, the terms "comprising," "containing," and "including" are inclusive, open-ended and do not exclude additional unrecited elements, compositional components or method steps. Accordingly, the terms "comprising" and "including" encompass the more restrictive terms "consisting of" and "consisting essentially of."

[0071] As used herein, the term "combination therapy" refers to the use of a composition described herein in combination with one or more additional treatment. Treatment in combination therapy can be any treatment such as any prophylactic agent, therapeutic agent (such as chemotherapy), radiotherapy, surgery and the like. The combination can refer to inclusion of a therapeutic or prophylactic agent in a same composition as a composition disclosed herein (for example, in the same capsule, tablet, ointment, etc.) or in separate compositions (for example, in 2 separate capsules). The separate compositions may be in a different dosage form. The use of the terms "combination therapy" and "in combination with" does not restrict the order in which a composition described herein and prophylactic and/or therapeutic agent and/or treatment are administered to a subject in need thereof. Compositions of the present disclosure can be administered prior to (e.g., 1 minute (min), 5 min, 15 min, 30 min, 45 min, 1 hour (h), 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 1 week (wk), 2 wk, 3 wk, 4 wk, 5 wk, 6 wk, 8 wk, 12 wk, 6 months (m), 9 m, or 1 year before), concomitant with, or subsequent to (e.g., 1 minute (min), 5 min, 15 min, 30 min, 45 min, 1 hour (h), 2 h, 4 h, 6 h, 8 h, 10 h, 12 h, 24 h, 36 h, 48 h, 72 h, 96 h, 1 week (wk), 2 wk, 3 wk, 4 wk, 5 wk, 6 wk, 8 wk, 12 wk, 6 months (m), 9 m, or 1 year after) administration of one or more prophylactic and/or therapeutic agent and/or treatment to a subject in thereof. Combination therapy as used herein can also refer to treatment of a subject having a single disease or multiple diseases, for example, prostate cancer in men and gynecomastia.

[0072] As used herein, the term "test sample" means sample of blood obtained from a subject. It is to be understood that when blood sample is obtained from a subject, subject's blood is used for determining the subject's endoxifen levels and/or other biomarkers that may be measured or tested. As used herein "plasma endoxifen" is used to refer to endoxifen levels in the subject's test sample, whether the test is conducted on whole blood, plasma or serum.

[0073] As used herein, the term "dosage form" means the form in which the compounds or compositions of the present disclosure are delivered to a patient.

[0074] As used herein, the term "pharmaceutically acceptable" or "pharmacologically acceptable" means materials, compositions, or vehicles that are compatible with other ingredients of the formulation and that they do not substantially produce adverse reactions, e.g., toxic, allergic, or immunological reactions, when administered to a subject. They may be approved by a regulatory agency, e.g., of the U.S. Federal or state government or listed in the U.S. pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans.

[0075] As used herein, the term "pharmaceutically acceptable carrier" or "carrier" means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent, or encapsulating material, involved in carrying or transporting one or more of the compounds of the present disclosure from one tissue, organ, or portion of the body or across the skin.

[0076] As used herein, the term "pharmaceutically acceptable salt" refers to any salt (e.g., obtained by reaction with an acid or a base) of a compound of the present disclosure that is physiologically tolerated in a subject (e.g., a mammal, and/or in vivo, ex-vivo, in vitro cells, tissues, or organs). A "salt" of a compound of the present disclosure may be derived from inorganic or organic acids and bases. Suitable anion salts include, arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, teoclate, fatty acid anions, and triethiodide.

[0077] Suitable cations include benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc.

[0078] For the purposes of this application, the salts of the compounds of the present disclosure are contemplated to be pharmaceutically acceptable for therapeutic uses. However, salts of acids and

bases that are non-pharmaceutically acceptable may also be useful, for example, in the preparation or purification of a pharmaceutically acceptable compound.

[0079] As used herein, the term "pharmaceutical composition" means a combination of the active agent (e.g., an active pharmaceutical compound or ingredient, API) with a carrier, inert or active (e.g., a phospholipid), making the compositions specially suitable for diagnostic or therapeutic uses *in vitro*, *in vivo*, or *ex vivo*.

[0080] As used herein "primary therapy" refers to a first line of treatment upon initial diagnosis of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in a subject. Exemplary primary therapies may involve surgery, a wide range of chemotherapies, and radiotherapy.

[0081] As used herein, the terms "subject," "patient," "participant," and "individual," may be used interchangeably herein and refer to a mammal such as a human. Mammals also include pet animals such as dogs, cats, laboratory animals, such as rats, mice, and farm animals such as cows and horses. Unless otherwise specified, a mammal may be of any gender or sex.

[0082] As used herein, the term "tamoxifen refractory" refers to a subject that has been dosed daily with tamoxifen for at least 2 days and has a level of plasma endoxifen of less than 30 nM (e.g., less than 20 nM, less than 25 nM, or less than 30 nM). As used herein, the term "tamoxifen resistance" refers to two classes of resistance: (a) de novo resistance, i.e., non-responsiveness to tamoxifen therapy from the beginning of the treatment, or (b) acquired resistance, i.e., non-responsiveness to tamoxifen therapy after initial responsiveness or tamoxifen-dependent growth /stimulated growth while continuing to express estrogen receptors (Minsun Chang. Biomol. Ther. 20(3), 256-267 (2012)). The acquired resistance to tamoxifen may develop as early as 3 m to 1 year to as late as 5 to 10 years. As used herein, the term "reference plasma endoxifen level" refers to a value of 30 nM.

[0083] As used herein, the term "unit dosage form" refers to physically discrete units suitable for unitary dosages for subjects, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[0084] It is specifically understood that any numerical value cited herein includes all values from the lower value to the upper value, i.e., all possible combination of numerical values between the lowest value and the highest value enumerated are to be considered to be expressly stated in this application and the endpoint of all ranges are included within the range and independently combinable. For example, if a concentration range or beneficial range is stated as 1% to 50%, it is intended that values such as 2% to 40%, 10% to 30%, or 1% to 3% etc., are expressly enumerated in

this specification. It is also to be understood that if a concentration or dose is stated as a specific value such as 1 mg or 10 mg, it is intended that it is intended to include 10% variation. As another example, a stated concentration of 20% is intended to include values ±10%. Yet another example, if a ratio of 1:10 to 10:1 is stated, then it is intended that ratios such as 1:9 to 9:1, from 1:8 to 8:1, from 1:7 to 7:1, from 1:6 to 6:1, from 1:5 to 5:1, from 1:4 to 4:1, from 1:3 to 3:1, from 1:2 to 2:1, from 1:1 to 2:1 or from 2:5 to 3:5 etc. are specifically intended. There are only some examples of what is specifically intended. Unless specified otherwise, the values of the constituents or components of the compositions are expressed in weight percent of each ingredient in the component.

[0085] All methods described herein can be performed in a suitable order unless otherwise indicated or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as" and "the like") is intended merely to illustrate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as any indicating any non-claimed element as essential to practice of the invention as used herein.

[0086] As used herein, the terms "hormone-dependent breast disorder," "hormone-dependent reproductive tract disorder," "hormone-dependent breast and reproductive tract disorder" each and collectively include, without limitation, any breast or reproductive tract (gynecologic) disorder that is related to or is sensitive to high estrogen or normal estrogen levels that need to be reduced, disorders with estrogen-receptor positive (ER+) and/or progesterone-receptor positive (PR+) disorders, for example, breast disorders, endometriosis, uterine fibroids (also called leiomyomas) etc. Reproductive tract disorders include endometrial, ovarian, cervical, uterus, vaginal, and vulvar cancers. The terms "estrogen-related disorder" and "estrogen-receptor related disorder" may be used interchangeably to refer to the foregoing hormone dependent disorders. The disorders may be presented primarily or secondarily to an underlying disease, for example, prostate cancer or other disorders such as liver diseases. Hormone-dependent breast and reproductive tract disorder include, for example, McCune-Albright syndrome, which is a disorder caused by a mutation in the GNAS gene affecting bones, skin, and several hormone-producing (endocrine) tissues, often resulting in abnormal scar-like (fibrous) tissue in their bones, a condition called polyostotic fibrous dysplasia, hyperthyroidism in individuals carrying such mutations, and in girls often resulting in precocious puberty.

[0087] As used herein, "breast disorder" means any aberration or a constellation of aberrations in the breast. Such aberration may be proliferative, non-proliferative, benign or malignant. Breast disorders include benign lesions of the breast (e.g., hyperplasia), increased breast density,

gynecomastia, mastalgia, and breast cancer. Benign breast lesions include, but are not limited to, hyperplasia, atypia, ductal hyperplasia, lobular hyperplasia, atypical ductal hyperplasia (ADH), and atypical lobular hyperplasia (ALH). While not cancerous, ADH and ALH may be indicative of a predisposition for breast cancer.

[0088] Breast density is a breast disorder identified by visual techniques such as mammography and reflects increased fibroglandular tissue within the breast, i.e., overgrowth of stromal and epithelial cells in the breast. Breast density is classified in 4 classes—Class A, B, C and D—based on the degree of severity of the density. It is an independent risk factor for breast cancer. At least 23 states in the USA require physicians to inform subjects if they have dense breast(s). There is currently no treatment for dense breasts, although subjects are reminded to make healthy lifestyle choices and undergo regular mammograms to monitor changes in breast.

[0089] Gynecomastia is a common male breast condition reflecting increased hyperplasia of the breast tissue, including epithelial hyperplasia, with prevalence of asymptomatic gynecomastia of 60% to 90% in neonates, 50% to 60% in adolescents, and up to 70% in men aged 50 to 69 years (Therapeutics and Clinical Risk Management 2011:7, 145 – 148). Newborn gynecomastia usually resolves itself within 4 weeks of birth and at least half of adolescent males experience gynecomastia with typical onset of 13 to 14 years of age (Tanner stage 3 or 4). Gynecomastia has been proposed to be a risk factor for male breast cancer.

[0090] Further, gynecomastia often presents itself secondarily to an underlying disorder such as prostate cancer, cirrhosis and liver disease, male hypogonadism, hyperthyroidism, renal failure and in patients undergoing hemodialysis, Type I diabetes mellitis, etc. Further, medications, such as anti-androgen medications or certain anti-psychotics, themselves have been reported to cause up to 25% of cases of gynecomastia and can be categorized by their hormone-like action. For example, the most common side effects attributed to bicalutamide, a nonsteroidal antiandrogen used for treatment of prostate cancer, are gynecomastia and breast pain.

[0091] As used herein, "breast cancer" means any malignant tumor of breast cells. Breast cancer may be at any stage of breast cancer, including stages of a pre-cancer, an early stage cancer, a non-metastatic cancer, a pre-metastatic cancer, a locally advanced cancer, and a metastatic cancer. There are several types of breast cancer. Exemplary breast cancers include, but are not limited to, ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), invasive (or infiltrating) lobular carcinoma (ILC), invasive (or infiltrating) ductal carcinoma (IDC), microinvasive breast carcinoma (MIC), inflammatory breast cancer, ER-positive (ER+) breast cancer, ER-negative (ER-) breast cancer, HER2+ breast cancer, triple negative breast cancer (TNBC), adenoid cystic (adenocystic)

carcinoma, low-grade adenosquamatous carcinoma, medullary carcinoma, mucinous (or colloid) carcinoma, papillary carcinoma, tubular carcinoma, metaplastic carcinoma, or micropapillary carcinoma. A single breast cancer tumor can be a combination of these types or be a mixture of invasive and in situ cancer.

[0092] DCIS is the most common non-invasive breast cancer. It involves the cell lining of the breast ducts. In DCIS, the cells have not spread beyond the walls of the duct into the surrounding breast tissue. About 1 in 5 new breast cancer cases will be DCIS. LCIS is a pre-cancerous neoplasia. It may be indicative of a predisposition for invasive cancer. LCIS only accounts for about 15% of the in situ (ductal or lobular) breast cancers.

[0093] IDC is the most invasive breast cancer. As the name applies, it is a carcinoma that begins in the breast ducts and then invades the surrounding fatty tissue. About 8 to 10 invasive breast cancers are infiltrating ductal carcinomas. IDC is often treated by surgery to excise the cancerous tissue, and radiation therapy. In addition, chemotherapy combined with immunotherapy (e.g., tamoxifen and tratuzumab) is often used to treat IDC. If the tumor is larger than 4 cm, then a radical mastectomy may be performed.

[0094] ILC is a cancer that develops in the lobules of the breast and has invaded the surrounding tissue. About 1 in 10 invasive breast cancer is an ILC. ILC is treated by surgery to excise the cancerous tissue, and radiation therapy. In addition, chemotherapy and immunotherapy combination (e.g., tamoxifen and tratuzumab) is often used as an adjuvant therapy to treat ILC.

[0095] Inflammatory breast cancer accounts for about 1% to 3% of all breast cancers. In inflammatory breast cancer, cancer cells block lymph vessels in the skin, resulting in the beast turning red and feeling warm. The affected breast may become larger or firmer, tender, or itchy. Inflammatory breast cancer is treated with chemotherapy, immunotherapy, radiation therapy and in some cases, surgery.

[0096] Estrogen Receptor positive (ER+) breast cancer is characterized by the presence of estrogen receptors on the surface of the cancerous cells. Growth of ER+ cancer cells is associated with the availability of estrogen (hormone-dependent or hormone sensitive breast cancer). Approximately, 80% of all breast cancers are ER+ breast cancers. Treatment options for ER+ breast cancer include chemotherapeutic agents that block estrogen (e.g., tamoxifen).

[0097] The present disclosure relates to methods of manufacturing stable preparations of (Z)-endoxifen free base, mixtures of (E)-endoxifen and (Z)-endoxifen (E/Z-mix), and salts thereof, and uses thereof. The present disclosure further relates to oral compositions comprising (Z)-endoxifen or salts thereof and methods of treating a subject in need thereof. The present disclosure also provides

methods of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract (gynecologic) disorder, or both by administering to the subject an oral composition comprising (Z)-endoxifen, E/Z-mix, or a salt thereof.

[0098] In an aspect, the present disclosure relates to oral compositions comprising endoxifen or salts thereof. Endoxifen comprised in compositions of the present disclosure may be (Z)-endoxifen, (E)-endoxifen or a combination thereof. In one aspect, the present disclosure relates to compositions comprising stable (Z)-endoxifen free base.

[0099] In one aspect, the present disclosure provides industrially scalable methods of making (Z)-endoxifen free base, mixtures of (E)-endoxifen and (Z)-endoxifen (E/Z-mix), and salts thereof. In an aspect, the industrially scalable methods are synthetic methods of making stable (Z)-endoxifen free base, E/Z-mix, and salts thereof. In another aspect, the present disclosure provides methods of making compositions comprising stable (Z)-endoxifen free base, E/Z-mix, and salts thereof.

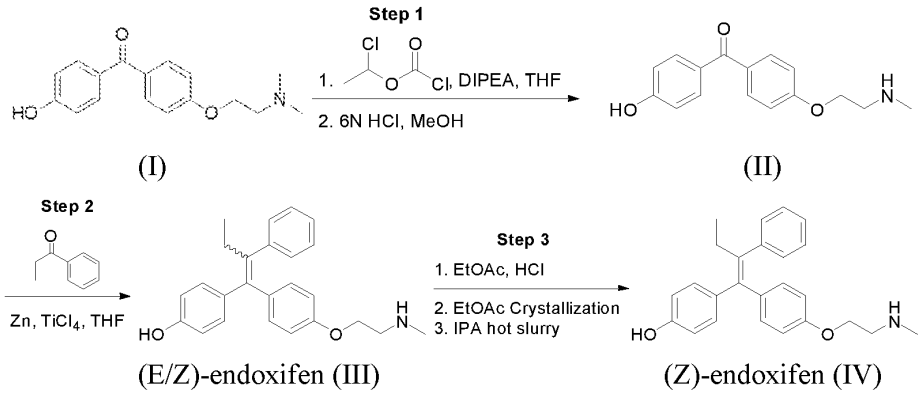
[0100] In certain aspects, the present disclosure provides crystalline forms of (Z)-endoxifen free base and crystalline forms of mixtures of (E)-endoxifen and (Z)-endoxifen, as well as pharmaceutical compositions of endoxifen comprising the crystalline forms described herein.

Synthesis of (Z)-endoxifen Free Base

[0101] Several methods for the synthetic preparation of endoxifen are known in the art. For e.g., methods of synthetic preparations of endoxifen and their prodrugs and salts are described in U.S. Patent No. 9,333,190 (Ahmad, Jina Pharmaceuticals); WO 2008/070463 (Ahmad, Jina Pharmaceuticals), U.S. Pub. No. 2010/0112041 (Ahmad, Jina Pharmaceuticals), WO 2012/050263 (Ahmad, Jina Pharmaceuticals), WO 2014/141292 (Desai, Intas Pharmaceuticals), WO 2017/070651 (USA/Alchem Lab. Corp.); WO 2009/120999A2 (Kushner), U.S. Patent No. 8,063,249 (Kushner, Olema Pharmaceuticals), U.S. Patent Nos. 7,531,578 and 8,119,695 (Forman and Yu), and WO 2012/050263 (Song, CJ Cheiljedang Corp).

[0102] Methods of synthetic preparation of endoxifen have also been published in research literature. (Gauthier *et al.*, J. Org. Chem, 61, 3890 – 3893 (1996), Fauq *et al.*, Bioorg Med Chem Lett. 2010 May 15;20(10):3036-3038); Stearns *et al.*, J. Natl. Cancer Inst. Vol 95, No. 23, 2003; Johnson *et al.*, Breast Cancer Research and Treatment. 85:151-159, 2004; Ogawa, et al. Chem. Pharm. Bull. 39, 911 – 916, 1991). However, there remains an unmet need for large scale industrial scalable manufacturing. Stable (Z)-endoxifen free base may be prepared accordance to **Schema 1** as further described below and in **Examples 1** to **9**.

Schema 1. ***Synthesis of (Z)-endoxifen Free Base***



Demethylation

[0103] In one aspect, the present disclosure relates to an industrially scalable process of making substantially purified (Z)-endoxifen free base, E/Z-mix, or salts thereof comprising demethylating the compound of Formula (I), [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone), (available from AstaTech Pharmaceuticals, Inc., China) to form the compound of Formula (II). Accordingly, in some embodiments, the industrial process comprises preparing the compound of Formula (II) by demethylating [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone) with a demethylating agent and a proton acceptor in an inert organic solvent to form the compound of Formula (II). The industrially scalable process for making the compound of Formula (II), (Z)-endoxifen free base, E/Z-mix, or salts thereof comprises demethylating the compound of Formula (I) in amounts ranging from 1 mg to 1000 kg per reaction.

[0104] In some embodiments, the compound of Formula (I) can be demethylated by reacting the compound of Formula (I) with a demethylating agent. The demethylating agent is any agent suitable for the purpose. Examples of suitable demethylating agents include N-iodosuccinamide (NIS), ethyl chloroformates (such as 1-chloroethyl chloroformate, dichloroethyl chloroformate, trichloroethyl chloroformate, α-Chloroethylchloroformate (ACE-Cl)), vinyl chloroformate (VO-Cl), cynogen bromide (BrCN: von Braun's reaction), diethyl azodicarboxylate, pyridinium chloride, and the like.

[0105] In some embodiments, the demethylating agent is a chloroformate selected from the group consisting of 1-chloroethyl chloroformate, dichloroethyl chloroformate, trichloroethyl chloroformate, α-Chloroethylchloroformate (ACE-Cl), and vinyl chloroformate (VO-Cl). In other embodiments, the demethylating agent is an ethyl chloroformate selected from the group consisting of selected from the group consisting of ethyl chloroformates, such as 1-chloroethyl chloroformate,

dichloroethyl chloroformate, trichloroethyl chloroformate, and α-Chloroethylchloroformate (ACE-Cl). In at least one embodiment, the demethylating agent is 1-chloroethyl chloroformate.

[0106] In some embodiments, a demethylating agent is added to the reaction mixture at a wt/wt ratio of the compound of Formula (I) to demethylating agent ranging from 1:0.5 to 1:10. In other embodiments, the demethylating agent is present at ratios (wt/wt) of the compound of Formula (I) to demethylating agent ranging from 1:2: to 1:5. In at least one embodiment, the demethylating agent is present at a ratio (wt/wt) of the compound of Formula (I) to demethylating agent of 1:2. In at least one embodiment, demethylating agent is present at a ratio (wt/wt) of the compound of Formula (I) to demethylating agent of 1:3.3. In other embodiments, the demethylating agent 1-chloroethyl chloroformate is present at a ratio (wt/wt) of the compound of Formula (I) to demethylating agent ranging from 1:0.5 to 1:10.

[0107] The demethylation reaction can be carried out in an inert organic solvent suitable for the demethylation reaction in the presence of a proton acceptor. Such inorganic solvents include dichloromethane, dichloroethane, chloroform, carbon tetrachloride, chlorobenzene, diethyl ether, 1,4-dioxane, tert-butyl methyl ether (TBME), tetrahydrofuran (THF), N,N-dimethylformamide (DMF), N-methylpyrrolidone (NMP), diglyme, nitromethane, 1,2-dimethoxyethane (DME), pyridine, acetone, acetonitrile, benzene, o-xylene, m-xylene, p-xylene, xylenes, hexanes, cyclohexane, heptane, octane, nonane, and decane, or a combination thereof. In an aspect, the industrially scalable process comprises one or more inert organic solvents for demethylation at a (wt/wt) ratio of the compound of Formula (I) to inert organic solvent ranging from 1:1 to 1:50. In some embodiments, the demethylation solvent is THF at a ratio of the compound of Formula (I) to THF (wt/wt) ranging from 1:1 to 1:50. In other embodiments, the THF is present in ratios (wt/wt) of the compound of Formula (I) to THF ranging from 1:1 to 1:20.

[0108] Proton acceptors suitable for the purpose of the present disclosure include, but are not limited to carbonates, such as sodium carbonate and potassium carbonate, and bicarbonates, such as sodium bicarbonate and potassium bicarbonate, proton sponge, and ethyldiisopropylamine, (N',N-diisopropyleamine, "DIPEA"). In an aspect, the industrially scalable process comprises a proton acceptor added to the reaction mixture at a wt/wt ratio of the compound of Formula (I) to proton acceptor ranging from 1:0.5 to 1:10. In some embodiments, the proton acceptor is present in a ratio (wt/wt) of the compound of Formula (I) to proton acceptor of 1:1:8.

[0109] One of skill in the art will be readily able to determine other solvents and proton acceptors known in the art suitable for demethylation reaction of the present disclosure.

[0110] Demethylating agents, solvents for demethylation reaction, and the compound of Formula (I) may be added in any order. Each reagent may be added to a suitable reactor in a single bolus or in multiple boluses and stirred.

[0111] In some embodiments, the compound of Formula (I) is charged to a suitable reactor to which inert organic solvent THF and proton acceptor DIPEA are added for demethylation reaction, and cooled to 0 °C to 20 °C, followed by addition of one or more demethylating agents. THF is added at a wt/wt ratio of 1:1 to 1:20, and proton acceptor DIPEA is added at a wt/wt ratio of 1:0.5 to 1:10 to the demethylation reaction mixture, where wt/wt is with respect to the compound of Formula (I). In some embodiments, the reaction mixture is cooled to not more than (NMT) 15 °C followed by slow addition of one or more demethylating agents. The reaction may be carried out under inert conditions, such as under nitrogen or argon.

[0112] The reaction mixture comprising the compound of Formula (I), one or more demethylating agents (for example, 1-chloroethyl chloroformate) in one or more inert organic solvents can be heated at temperature ranging from 20 °C to 250 °C, such as from 40 °C to 80 °C, from 50 °C to 230 °C, from 50 °C to 120 °C, and from 150 °C to 200 °C. In some embodiments, the reaction mixture is heated under reflux. In other embodiments, the compound of Formula (I) is reacted with demethylating agent and proton acceptor for not less than (NLT) 5 hours, NLT 8 hours, NLT 12 hours, NLT 24 hours, NLT 36 hours, NLT 48 hour and NLT 72 hours. In at least one embodiment, the reaction is heated under reflux NLT 12 hours. The reaction may be held and stored until further use. In some embodiments, the reaction mixture is held not more than (NMT) 24 hours under reflux conditions while stirring.

[0113] The mixture can be subjected to one or more rounds of distillation under reduced pressure. Distillation may be carried out at NMT 100 °C, at NMT 95 °C, at NMT 90 °C, at NMT 85 °C, at NMT 80 °C, or at NMT 70 °C with solvents suitable for distillation such as ethyl acetate, lower alcohols (non-limiting examples include methanol, ethanol, n-propanol, and isopropanol), benzene, acetone, acetonitrile, toluene, dichloromethane, 1,2-dichloroethane, and chloroform. One of skill in the art will be able to readily determine additional suitable solvents useful for the purpose.

[0114] In at least one embodiment, the solvent used for distillation is methanol. As a non-limiting example, methanol may be used for solvent swap for 2 to 5 rounds of distillation under reduced pressure.

[0115] Solvents, such as methanol, may be used for distillation at a (wt/wt) ratio of the compound of Formula (I) to solvent ranging from 1:1 to 1:10 per round of distillation.

[0116] Then, the mixture can be reacted with a solvent/acid mixture by addition of an acid (wt/wt ratio of the compound of Formula (I) to acid ranging from 1:1 to 1:10) to the solvent while stirring and heating under reflux. The acid can be any suitable acid. HCl is an example of acid suitable for the purpose of the present disclosure. Non-limiting examples of suitable solvent/acid mixtures include methanol/HCl, ethanol/HCl, propanol/HCl, isopropanol/HCl, methanol/sulfuric acid, methanol/phosphoric acid, ethanol/sulfuric acid, ethanol/phosphoric acid, propanol/sulfuric acid, propanol/phosphoric acid, isopropanol/sulfuric acid, isopropanol/phosphoric acid, methanol/acetic acid, ethanol/acetic acid, propanol/acetic acid, isopropanol/acetic acid, methanol/formic acid, ethanol/formic acid, propanol/formic acid, and isopropanol/formic acid. In at least one embodiment, the solvent/acid mixture is methanol/6N HCl. As a non-limiting example, methanol in methanol/HCl mixture may be added at a wt/wt ratio of the compound of Formula (I) to methanol in solvent/acid mixture at 1:3.2 while HCl in the methanol/HCl mixture may be at a wt/wt ratio of the compound of Formula (I) to HCl in the solvent/acid mixture at 1:4. In at least one embodiment, the methanol/6N HCl mixture is added at a wt/wt ratio of the compound of Formula (I) to methanol/6N HCl ranging from 1:1 to 1:10, such as 1:1 to 1:5.

[0117] Distillation may be carried out for NLT 5 hours, NLT 8 hours, NLT 10 hours, NLT 12 hours, NLT 14 hours under reduced pressure. Distillation may be carried out at a temperature NMT 70 °C, NMT 75 °C, NMT 80 °C, NMT 85 °C, NMT 90 °C and NMT 90 °C.

[0118] The reaction mixture may be held and stored until further use. In some embodiments, the reaction mixture may be held for NMT 24 hours under reflux conditions while stirring.

[0119] The reaction mixture can be neutralized with a neutralizing agent such as sodium hydroxide (NaOH), ammonium hydroxide, aminomethylpropanol and the like, and filtered. The resulting wet cake can be washed with water and an organic solvent such as ethyl acetate (EtOAc) to obtain (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl)methanone, the compound of Formula (II).

[0120] The neutralizing agent may be at a wt/wt ratio of the compound of Formula (I) to the neutralizing agent ranging from 1:1 to 1:10. In some embodiments, the neutralizing agent is 8N sodium hydroxide at a ratio ranging from 1:1 to 1:10. In other embodiments, the neutralizing agent is 8N sodium hydroxide at a ratio ranging from 1:2 to 1:8.

[0121] In another aspect, the industrially scalable process for making (Z)-endoxifen free base, E/Z-mix or salts thereof comprises one or more steps of washing filtered product (the compound of Formula (II)) with purified water (1:1 to 1:5 wt/wt) and organic solvents such as ethyl acetate (EtOAc) (1:0.5 to 1:10 wt/wt) wherein the wt/wt is with respect to the compound of Formula (I).

The wet cake is dried under reduced pressure/vacuum. The temperature for can range from 25 °C to 60 °C. In some embodiments, the drying is carried out at a temperature NMT 50 °C.

McMurry Reaction

[0122] In another aspect, the present disclosure relates to an industrially scalable process of making (Z)-endoxifen free base, E/Z-mix, and salts thereof comprising subjecting the compound of Formula (II) to a McMurry reaction to afford an E/Z-mix (i.e., a mixture of (E)-endoxifen and (Z)-endoxifen free bases), compounds of Formula (III).

[0123] The McMurry reaction has been used to prepare tamoxifen (European Patent Application No. 168175). The present disclosure relates to an industrially scalable process wherein the compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, is coupled to propiophenone mediated by a McMurry reaction via titanium salts such as chloride salts of titanium (for example, titanium trichloride and titanium tetrachloride ($TiCl_4$)) and reducing agents in inert organic solvents to form an E/Z mix of compounds of Formula (III).

[0124] Salts of titanium that are useful for the present disclosure include titanium halides (such as titanium trichloride ($TiCl_3$), Titanium tetrachloride ($TiCl_4$), titanium iodides, titanium bromides, and titanium fluorides), titanium (IV) trichloride isopropoxide, and titanium isopropoxide. In some embodiments, the titanium salt is $TiCl_4$. Titanium salts, such as $TiCl_4$, are added at a wt/wt ratio of the compound of Formula (II) to titanium salt ranging from 1:0.1 to 1:12.

[0125] Reducing agents include zinc, zirconium, vanadium, niobium, molybdenum, tungsten, aluminum, magnesium, potassium, zinc-copper couple, alkali and alkali earth metals, butylium, lithium, and lithium aluminum hydride. In at least one embodiment, the reducing agent is zinc. The McMurry synthesis is conveniently carried out using a reducing agent such as zinc at a wt/wt ratio of the compound of Formula (II) to reducing agent ranging from 1:0.1 to 1:10. In some embodiments, the ratio of reducing agent is in excess compared to titanium salts.

[0126] The McMurry synthesis can be carried out in one or more inert organic solvents. Inert organic solvents useful for the McMurry reaction include dichloromethane, dichloroethane, chloroform, carbon tetrachloride, chlorobenzene, diethyl ether, 1,4-dioxane, tert-butyl methyl ether (TBME), tetrahydrofuran (THF), N,N-dimethylformamide (DMF), N-methylpyrrolidone (NMP), diglyme, nitromethane, 1,2-dimethoxyethane (DME), pyridine, acetone, acetonitrile, benzene, o-xylene, m-xylene, p-xylene, xylenes, hexanes, cyclohexane, heptane, octane, nonane, and decane, or a combination thereof. In some embodiments, the inert organic solvent is at wt/wt ratio of the compound of Formula (II) to solvent ranging from 1:1 to 1:50. In other embodiments, the inert

organic solvent is at wt/wt ratios of the compound of Formula (II) to solvent ranging from 1:1 to 1:20. In some embodiments, the inert organic solvent used for the McMurry reaction is THF. THF, in some embodiments, is at wt/wt ratio of the compound of Formula (II) to THF ranging from 1:1 to 1:20.

[0127] It is advantageous to combine titanium salts and reducing agent in the inert organic solvents to create a pre-mix. Titanium salts are added to the reducing agent and inert organic solvents at such a rate so as to keep the internal temperature at NMT 75 °C, such as NMT 65 °C, NMT 55 °C, NMT 45 °C, NMT 40 °C, NMT 35 °C, NMT 30 °C, NMT 25 °C, NMT 20 °C, and NMT 15 °C. Accordingly, titanium salts and reducing agent in the inert organic solvents are combined to create a pre-mix. In some embodiments, Zn, $TiCl_4$ and THF are combined to create $Zn/TiCl_4$/THF mixture. In at least one embodiment, $TiCl_4$ is added to Zn and THF and mixed keeping the internal temperature NMT 20 °C for NLT 10 min.

[0128] Preparation of titanium salt and a reducing agent in an inert organic solvent may further comprise heating titanium salt and reducing agent in an inert organic solvent to a temperature ranging from 20 °C to 250 °C, such as from 40 °C to 80 °C, from 50 °C to 230 °C, from 50 °C to 120 °C, and from 150 °C to 200 °C. In some embodiments, titanium salt and reducing agent present in an inert organic solvent are heated at NLT 60 °C. In some embodiments, preparation of titanium salt and a reducing agent in an inert organic solvent further comprises heating titanium salt and reducing agent in an inert organic solvent under reflux. Titanium salt and reducing agent in inert organic solvent are heated under reflux for NLT 30 min, such as NLT 1 hour, NLT 2 hours, NLT 4 hours, NLT 6 hours and NLT 8 hours, under inert conditions such as under N_2 or argon.

[0129] It is also advantageous to pre-mix the compound of Formula (II) with inert organic solvent such as THF and propiophenone and then reacting the compound of Formula (II) to pre-mixed reducing agent/titanium salt/solvent mixture such as a $Zn/TiCl_4$/THF mixture to form a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III). Propiophenone can be added at a wt/wt ratio of the compound of Formula (II) to propiophenone ranging from 1:0.01 to 1:5. Inert organic solvent can be at a wt/wt ratio of the compound of Formula (II) to solvent ranging from 1:1 to 1:20. The compound of Formula (II) of step (a) is reacted with titanium salt and a reducing agent in an organic solvent under reflux for NLT 0.5 hours, NLT 1 hour, NLT 2 hours, NLT 4 hours, NLT 6 hours, NLT 8 hours, NLT 12 hours, NLT 24 hours, and NLT 48 hours. In at least one embodiment, the compound of Formula (II) is mixed with THF and propiophenone and reacted to a pre-mixture of Zn, $TiCl_4$, THF and heat under reflux for NLT 2 hours. In another embodiment, the compound of Formula (II) is mixed with THF and propiophenone and reacted to the $Zn/THF/TiCL_4$

mixture as described above and heated under reflux for NLT 8 hours. The reaction mixture may then be allowed to cool to 0 °C to 35 °C.

[0130] The mixture of (E)-endoxifen and (Z)-endoxifen in the reaction mixture can be then subjected to extractive purification, distillation and crystallization to afford a purified mixture of (E)-endoxifen and (Z)-endoxifen. The mixture of (E)-endoxifen and (Z)-endoxifen in the reaction mixture can be subject to extractive purification by extracting with inert organic solvents, such as THF and MeTHF, or by addition of salts, such as potassium carbonate, ammonium chloride, sodium chloride, sodium hydroxide, to the reaction mixture and extraction with an inert organic solvent, such as THF and MeTHF.

[0131] In some embodiments, the reaction mixture is extracted one or more times with ammonium chloride, such as 25% ammonium chloride (1:1 to 1:30 wt/wt); silica (Celite®) bed (1:0.01 to 1:5 wt/wt); and/or solvent, such as THF (1:1 to 1:10 wt/wt). In other embodiments, the reaction mixture is extracted one or more times with potassium carbonate (K_2CO_3), such as 40% K_2CO_3 (1:1 to 1:10 wt/wt) and MeTHF (1:1 to 1:10 wt/wt). In some embodiments, the E/Z mixture may be further extracted with NaOH, such as 1N NaOH (1:1 to 1:20 wt/wt). In at least one embodiment, NaCl (1:0.1 to 1:0.5 wt/wt) may be added to 1N NaOH for the extraction step.

[0132] In some embodiments, the reaction mixture may be further extracted one or more times with THF or MeTHF. In at least one embodiment, the reaction mixture is extracted 3 or more times with MeTHF. The applicants have found MeTHF to be surprisingly suitable for the step of extraction of a mixture of (E)-endoxifen and (Z)-endoxifen, affording higher yields of purified mixtures of (Z)-endoxifen and (E)-endoxifen. In at least one embodiment, the mixture may be still further extracted with 20% sodium chloride (1:1 to 1:10 wt/wt).

[0133] The reaction mixture can be next subjected to 2 to 5 rounds of solvent swap and distillation with a suitable solvent, such as ethyl acetate, IPA, and IPA/PPW (1:1 to 1:10 wt/wt with respect to the compound of Formula (III)). Distillation may be carried out under reduced pressure/vacuum at temperatures ranging from 30 °C to 90 °C. In some embodiments, the distillation may be performed at temperature NMT 30 °C, NMT 35 °C, NMT 40 °C, NMT 45 °C, NMT 50 °C, NMT 55 °C, NMT 60 °C, NMT 65 °C, NMT 70 °C, NMT 75 °C, NMT 80 °C and NMT 90 °C, and filtered. The filtered product may be washed with solvents such as EtOAc, IPA, IPA/PPW or n-heptane and then crystallized with crystallization systems such as EtOAc/n-heptane (1:2 v/v) or IPA/n-heptane (1:2.7 v/v) at a wt/wt ratio of a compound of Formula (III) to EtOAc/n-heptane or IPA/n-heptane ranging from 1:1 to 1:20 and dried, for example, at NMT 60 °C, to afford a crystalline solid mixture of (E)-endoxifen and (Z)-endoxifen free bases, compounds of Formula (III).

[0134] In yet another aspect, the present disclosure relates to an industrially scalable method of manufacturing or reequilibriating an E/Z-mix having an E/Z ratio of approximately 1:1 (45:55 to 55:45). A suitable reactor may be charged with the compounds of Formula (III) dissolved in an inert organic solvent, such as ethyl acetate, prepared in a McMurry reaction as described above. The compounds of Formula (III) can have an E/Z ratio of 99:1 to 60:40. The mixture can be concentrated at temperatures ranging from 40 °C to 85 °C. In some embodiments, the mixture is concentrated at temperature NMT 75 °C until the volume reaches 5 vol. The mixture is heated to reflux and then cooled to temperatures ranging from 40 °C to 60 °C. In some embodiments, the temperature of the mixture is cooled to 50±5 °C. n-heptane, at a ratio of the compounds of Formula (III) to n-heptane ranging from 1:1 to 1:20, may be added slowly to the mixture and the mixture may be then cooled to 0±5 °C. The mixture may be stirred at 0±5 °C for NLT 0.5 hours, such as NLT 1 hour, NLT 2 hours, NLT 4 hours, NLT 8 hours, NLT 12 hours or NLT 24 hours. The mixture may be filtered and washed with ethyl acetate /n-Heptane (1:2 v/v) at a wt/wt ratio of the compounds of Formula (III) to ethyl acetate/n-heptane ranging from 1:1 to 1:10. The wet cake may be dried under reduced pressure to afford E/Z-endoxifen mixture having an E/Z-ratio of approximately 1:1. Drying may be carried out at temperatures ranging from 30 °C to 70 °C. In at some embodiments, the wet cake is dried under reduced pressure or vacuum at NMT 60 °C to afford E/Z-endoxifen mixture having an E/Z-ratio of approximately 1:1 (45:55 to 55:45).

[0135] In still another aspect, the compounds of Formula (III) may be further purified or enriched or reequilibrated to obtain substantially pure (Z)-endoxifen as described below.

Enrichment Purification of (Z)-endoxifen Free Base

[0136] In still another aspect, the present disclosure relates to industrially scalable methods of manufacturing by enrichment and purification (Z)-endoxifen free base. Industrially scalable enrichment and purification of (Z)-endoxifen may be carried out as described herein using the method of Step 3 of exemplary **Schema 1**, and as further described in **Examples 1, 2, 4,** and **9**. The starting mixture of (E)-endoxifen and (Z)-endoxifen used for fractional crystallization can have any E/Z ratio, for example, E/Z ratio ranging from 99:1 to 1:10. In some embodiments, the E/Z-ratio of the starting (E)/(Z)-endoxifen mixtures ranges from 30:70 to 70:30. In some embodiments, the E/Z-ratio of the starting (E)/(Z)-endoxifen mixtures ranges from 99:1 to 1:99. In some embodiments, the E/Z-ratio of the starting (E)/(Z)-endoxifen mixtures is 51:1, 1:1.8 or 1:5.6.

[0137] The E/Z-mix can be the compounds of Formula (III) obtained as described above or it can be commercially sourced (for example, from Sigma-Aldrich). A mixture of (E)-endoxifen and (Z)-

endoxifen (E/Z-mix) is subjected to fractional crystallization to obtain a first crystalline solid and a first mother liquor enriched with (Z)-endoxifen free base (Example 1). Fractional crystallization is carried using a first solvent which is capable of triturating endoxifen and its derivatives such that (Z)-endoxifen tends to remain in filtrate. Suitable first solvents are those that differentially solubilize the endoxifen isomers, and include, without limitation, ethyl acetate, isopropanol, isopropanol/PPW, acetonitrile, acetonitrile/PPW, and dichloromethane. In some embodiments, the first solvent is ethyl acetate. The first solvent, for example, ethyl acetate, is added at a wt/wt ratio of the compounds of Formula (III) to first solvent ranging from 1:1 to 1:20. In some embodiments, the the compounds of Formula (III) are dissolved in first solvent, and heated to a temperature ranging from 50 °C to 80 °C and cooled to NMT 35 °C.

[0138] It has been a surprising discovery that acidification of the mixture enhances the conversion of (E)-endoxifen to (Z)-endoxifen. Accordingly, in some embodiments, the compounds of formula (III) are pretreated with an acid and then neutralized with a base.

[0139] As a non-limiting example, a suitable reactor is charged with the compounds of Formula (III) to which first solvent is added and cooled to 0 °C – 5 °C. Next, an acid such as HCl or TFA may be added slowly. In some embodiments, the acid is added to the E/Z-endoxifen mixture at a wt/wt ratio of the compounds of Formula (III) to acid ranging from 1:1 to 1:5. The reaction mixture may then be heated at temperatures ranging from 50 °C to 70 °C while stirring. In some embodiments, the reaction is carried out under reflux. The reaction may be carried out for NLT 4 hours, such as NLT 6 hours, NLT 12 hours, NLT 24 hours, and NLT 48 hours. The reaction mixture is cooled to 0 °C – 5 °C and neutralized with a neutralizing agent.

[0140] In some embodiments, the neutralizing agent is added to the reaction mixture at a wt/wt ratio of the compounds of Formula (III) to neutralizing agent ranging from 1:1 to 1:5. Suitable neutralizing agents include sodium hydroxide, potassium hydroxide, ammonium hydroxide, aminomethylpropanol, and the like. In some embodiments, the neutralizing agent is 8N sodium hydroxide. The pH of the reaction mixture is preferably alkaline. In some embodiments, the pH is $\geq$ 10, such as $\geq$ 11 or $\geq$ 12.

[0141] In some embodiments, (Z)-endoxifen is extracted into the organic layer and collected, and the aqueous phase is washed one or more times with the first solvent such as ethyl acetate (added at a wt/wt ratio of the compounds of Formula (III) to first solvent ranging from 1:1 to 1:10). The organic layers are pooled, and washed one or more times with brine (20% NaCl; added at a wt/wt ratio of the compounds of Formula (III) to NaCl ranging from 1:1 to 1:10). The organic layer is treated with activated carbon and filtered over silicon dioxide (Celite®) bed (added at a wt/wt ratio

of the compounds of Formula (III) to silica ranging from 1.01 to 1:0.1). The product is washed again one or more times with first solvent (added at a wt/wt ratio of the compounds of Formula (III) to first solvent ranging from 1:1 to 1:10), and distilled. Distillation may be carried out at temperatures ranging from 50 °C to 80 °C. In some embodiments, the temperature may be NMT 75 °C.

[0142] The first mother liquor is enriched in (Z)-endoxifen as seen in **Example 1** and **Tables 2** and **3**. In some embodiments, the first mother liquor is enriched by at least 50% as compared to with the E/Z-ratio of the mixture of E-endoxifen and Z-endoxifen. In other embodiments, the first mother liquor is enriched in (Z)-endoxifen by at least 70% as compared to the E/Z-ratio of the mixture of E-endoxifen and Z-endoxifen.

[0143] The first mother liquor may be subjected to recrystallization by concentrating the first mother liquor, or swapping out the first solvent from the first mother liquor one or more times to obtain second crystalline solid and a second mother liquor (**Table 5**). Recrystallization is carried out using a second solvent for swapping. The second solvent is added at a wt/wt ratio of the compounds of Formula (III) to second solvent ranging from 1:1 to 1:10 to create a slurry. Suitable second solvents include IPA, IPA/PPW, acetone, acetone/MTBE, ethanol, EtOAc, EtOAc/n-heptane. In some embodiments, the second solvent is IPA. Surprisingly, IPA has been found to triturate (Z)-endoxifen into solid fraction at levels higher than EtOAc. Accordingly, in some embodiments, when the first solvent is EtOAc, the second solvent is IPA or IPA/PPW. This is useful in directing (Z)-endoxifen first into the filtrate (first mother liquor) from EtOAc, and then into the solid fraction from IPA or IPA/PPW. In at least one embodiment, the second solvent is IPA/PPW (**Table 7**). In yet another embodiment, the second solvent is acetone/MTBE. The second crystalline solid is (Z)-endoxifen, (Z)-4-(1-(4-(2-(methylamino)ethoxy)phenyl)-2-phenylbut-1-enyl)phenol, the compound of Formula (IV). (Molecular weight 373.49; Molecular formula: $C_{25}H_{27}NO_2$; Melting point 139 °C – 143 °C. The second crystalline solid is ≥70% (Z)-endoxifen, such as ≥75% (Z)-endoxifen, ≥80% (Z)-endoxifen or ≥90% (Z)-endoxifen. In some embodiments, the second crystalline solid is ≥90% (Z)-endoxifen.

[0144] The second crystalline solid may optionally be subjected to recrystallization to obtain a third crystalline solid, (Z)-endoxifen (**Table 5**). The third crystalline solid may be ≥90% (Z)-endoxifen, such as ≥91% (Z)-endoxifen, ≥92% (Z)-endoxifen, ≥93% (Z)-endoxifen, ≥94% (Z)-endoxifen, ≥95% (Z)-endoxifen, ≥96% (Z)-endoxifen, ≥97% (Z)-endoxifen, ≥98% (Z)-endoxifen, or ≥99% (Z)-endoxifen. In some embodiments, the third crystalline solid is ≥90% (Z)-endoxifen. In some embodiments, the third crystalline solid is ≥95% (Z)-endoxifen. This optional recrystallization is

carried out using a third solvent. The third solvent is selected from the group consisting of ethanol, methanol, ethyl acetate, IPA, IPA/PPW, acetone, acetone/MTBE and EtOAc/n-heptane.

[0145] In an aspect, the present disclosure relates to pre-heating first solvent, second solvent, and third solvent prior to use (**Table 2**). In some embodiments, one or more of the first solvent, second solvent, and third solvent can each be independently preheated to a temperature ranging from 40 °C to 80 °C. Fractional crystallization and recrystallization steps may also include steps of distilling at 60 °C to 80 °C and/or cooling the resulting solution to a temperature ranging from 0 °C to 35 °C.

[0146] It is to be understood that in some embodiments, first, second, and third crystalline solids as well as the second mother liquor obtained as described above may be further subjected to fractional crystallization and recrystallization as described above one or more time to obtain purified (Z)-endoxifen. It is also to be understood that first, second, and/or third crystalline solids obtained may be optionally reprocessed using column chromatography techniques to obtain more (Z)-endoxifen.

[0147] In certain embodiments, the industrially scalable methods described herein independently comprises additional steps or procedures (e.g., to remove reaction by-products, or to workup, isolate or purify reaction products) as detailed in examples herein. In some embodiments, the (Z)-endoxifen free base has <2%, <1%, and <0.5% impurity. In other embodiments, the compounds of Formula (III) have <2%, <1%, and <0.5% impurity.

[0148] A person of skill in the art will recognize several parameters of the foregoing process that may be varied in order to obtain a desirable outcome. These parameters include for example, the methods and means of purification of reaction components and solvents; the order of addition of said reaction components and solvents to the reaction mixture, duration of reaction of said reaction components and solvents; and temperature and rate of stirring, mixing or agitation of the reaction components and solvents during the reactions.

[0149] It was found that the process embodied by the methods herein (also including the particular process steps) fulfills one or more of the following criteria: better stability, safer, simpler, higher yielding and more economical when compared with the known processes for manufacturing compounds of Formula (II), (III) and (IV). (Z)-Endoxifen prepared by the processes disclosed below is stable for at least 9 months at 5 °C and 25 °C at 60% relative humidity (25 °C/60% RH) and for at least 3 moths at 40 °C/75% RH (**Example 9**). Stability at elevated temperatures is indicative of long term stability. Accordingly, (Z)-endoxifen free base prepared by the processes of the present disclosure are stable for at least 6 months, such as for at least 9 months, at least 12 months, or at least 18 months. Further, the process described herein is considered scalable in multi-kilogram operations, making it suitable for commercial production.

Endoxifen Salts

[0150] In still another aspect, the present application provides endoxifen salts and methods of making endoxifen salts. Endoxifen salts known in the art include hydrochloride (Fauq *et al.*, Bioorg Med Chem Lett. 2010 May 15;20(10):3036-3038) and citrate salts of endoxifen (U.S. Patent No. 9333190; U.S. Publication No. 2010/0112041) and are being evaluated for oral administration to subjects.

[0151] In certain embodiments, the present disclosure provides anion salts of endoxifen selected from the group consisting of arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, Teoclate, and triethiodide.

[0152] In other embodiments, the present disclosure provides cation salts of endoxifen selected from the group consisting of benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc.

[0153] The endoxifen salts of the present disclosure may be made using any of the compounds of Formulae (I), (II), (III) and (IV), prepared as described above.

Endoxifen Gluconate

[0154] In some embodiments, the present disclosure provides a gluconate salt of endoxifen, or a chemical equivalent thereof. Accordingly, in at least one embodiment, the endoxifen comprised in a composition of the present disclosure is an endoxifen gluconate or a chemical equivalent thereof. Unless specified otherwise, it will be understood that when referring to endoxifen gluconate herein, its chemical equivalents will also be encompassed.

[0155] For the purposes of the present disclosure, chemical equivalents of endoxifen gluconate include all anionic, cationic, and non-ionic reaction complexes between the endoxifen molecule and the gluconate moiety. Such complexes typically react with the hydroxyl group of the endoxifen molecule. The gluconate moiety includes D-gluconic acid, gluconic acid, glycogenic acid, glycan-Δ-lactone, and the like. In some embodiments, the gluconate moiety is a pharmaceutically acceptable gluconate salt. Such salts include calcium gluconate, sodium gluconate, and salts of alkali metals

and alkaline earth metals such as potassium gluconate, magnesium gluconate, lithium gluconate, and the like.

[0156] Both stereoisomers of gluconate, the D-form and the L-form, are embraced in the present disclosure. In some embodiments, endoxifen gluconate comprised in the compositions of the present disclosure is selected from the group consisting of (Z)-endoxifen D-gluconate, (Z)-endoxifen L-gluconate, (E)-endoxifen D-gluconate, (E)-endoxifen L-gluconate and combinations thereof. In some embodiments, the pharmaceutical composition comprises (Z)-endoxifen L-gluconate. In certain embodiments, the pharmaceutical composition comprises (Z)-endoxifen D-gluconate. The compositions may be present as racemic mixtures, pure stereoisomers (e.g., enantiomers and diastereoisomers), stereo-enriched mixtures and the like unless otherwise indicated. When a particular stereoisomer is shown or named herein, it will be understood by those skilled in the art that minor amounts of other stereoisomers may be present in the compositions of the present disclosure unless otherwise indicated, provided that the utility of the composition as a whole is not eliminated by the presence of such other isomers. Individual isomers may be obtained by numerous methods that are well known in the art, including chiral chromatography using a suitable chiral stationary phase or support, or by chemically converting them into diastereoisomers, separating the diastereoisomers by conventional means such as chromatography or recrystallization, then regenerating the original stereoisomer.

[0157] The present disclosure also includes methods of making endoxifen gluconate or a chemical equivalent thereof, which includes mixing endoxifen with a gluconate moiety to yield endoxifen gluconate. Methods of making gluconate salts of therapeutic agents are known in the art (for example, U.S. Publication No. 2002/0127665).

[0158] In some embodiments, an endoxifen D-gluconate (such as (Z)-endoxifen D-gluconate) salt may be obtained by mixing an ethanolic slurry of the endoxifen (such as (Z)-endoxifen prepared by the methods described above) as the free base with an aqueous solution of D-gluconic acid, obtained by hydrolyzing a 20% w/v solution of D-gluconolactone in water by heating at 70 °C for 15 to 30 min. In some embodiments, a minimum volume of ethanol is used and 5 ml of the aqueous D-gluconic acid solution is added per 1 g of endoxifen free base. Stirring is then continued until a clear solution is obtained. The required volume of this solution is then added to one or more of other excipients to produce formulations in which the “active ingredient” is (Z)-endoxifen D-gluconate or (Z)-endoxifen L-gluconate salt. The salt may be purified by any of the methods known in the art and disclosed herein.

[0159] Purified (Z)-endoxifen free base or a mixture of (E)/(Z)-endoxifen is both useful for the purpose of preparation of the endoxifen gluconate salt. A solution of (Z)-endoxifen D-gluconate or (Z)-endoxifen L-gluconate may also be purified from a mixture of (E)/(Z)-endoxifen gluconate salt as described herein by fractional crystallization or recrystallization (**Examples 1-3**) to obtain a solid purified (Z)-endoxifen salt. The solid salt may be stored at -5 °C under N_2 until further use.

[0160] It will be understood by those skilled in the art that other endoxifen salts can also be used as starting material with gluconate moiety or gluconate salts to yield endoxifen gluconate or chemical equivalents thereof.

[0161] Endoxifen gluconate or chemical equivalent thereof may be prepared using (Z)-endoxifen prepared as described above or with starting reactants that are readily available. For example, crude endoxifen HCl (≥98%) and sodium gluconate are readily available from Sigma-Aldrich, USA.

[0162] In some embodiments, endoxifen HCl and sodium gluconate are dissolved in a suitable solvent to yield endoxifen gluconate or a chemical equivalent thereof. In at least one embodiment, the composition comprising endoxifen gluconate also comprises endoxifen HCl. In other embodiments, an (E)/(Z)-endoxifen mixture (compounds of Formula (III)) and sodium gluconate are dissolved in a suitable solvent to afford endoxifen gluconate or a chemical equivalent thereof.

[0163] Suitable solvents for making endoxifen gluconate or chemical equivalents thereof include, but are not limited to, organic solvents such as alcohols, acetones, DMSO, polyethylene glycol, fatty acids and fatty alcohols and their derivatives, hydroxyl acids, pyrrolidones, urea, vegetable oils, animal oils such as fish oils, essential oils, and the like or mixtures thereof, and water-miscible solvents such as water miscible alcohols, dimethylsulfoxide, dimethylformamide, water-miscible ether, for example, tetrahydrofuran, water-miscible nitrile, for example acrylonitrile, a water miscible ketone such as acetone or methyl ethyl ketone, an amide such as dimethylacetamide, propylene glycol, glycerin, polyethylene glycol 400, glycofurol, tetraglycol, and the like, or mixtures thereof.

[0164] Water-miscible solvents useful for the preparation of endoxifen gluconate are glycerin, ethanol, propanol, isopropanol, propylene glycol, polyethylene glycols, or mixtures thereof. Additional solvents that are useful include diglycol monoethyl ether (transcutol); alkelene glycols, such as dipropylene glycol, propylene glycol, polyethylene glycols such as PEG 300, 400, 3395, 4450 and the like; dimethyl isosorbide; and dehydrated alcohol. In some embodiments, the solvent is a dehydrated alcohol, such as absolute alcohol. In certain embodiments, the amount of solvent is sufficient to dissolve the endoxifen (free base, salts) and gluconate salts. The concentration of the

solvent can also be adjusted as needed. The reaction can be carried out at room temperature and at atmosphere of pressure.

[0165] The amount of endoxifen free base or endoxifen salt (such as endoxifen HCl and the like) and gluconate salt (such as and sodium gluconate and the like) that can be used to make endoxifen gluconate or chemical equivalent thereof can vary depending on the amount of reactants used. The resulting endoxifen gluconate will have endoxifen:gluconate moiety at 1:1 ratio.

[0166] In some embodiments, the amount of endoxifen or endoxifen salt used for making endoxifen gluconate is from 0.01% to 40% (e.g., from 1% to 10%, or from 3% to 5%) by weight of the total composition (wt/wt). In some embodiments, the gluconate salt used for making endoxifen gluconate is from 0.01% to 40% (wt/wt) (e.g., from 1% to 10% (wt/wt), or from 3% to 5% (wt/wt)). One of skill in the art will be guided by skill and knowledge in the field and the present disclosure, including without limitation, amounts of reactants which are effective to achieve the desired yields.

Crystalline Forms

[0167] In certain aspects, the present disclosure provides crystalline forms of endoxifen, including crystalline forms of (Z)-endoxifen free base and crystalline forms of mixtures of (E)-endoxifen and (Z)-endoxifen. The present disclosure further provides pharmaceutical compositions of endoxifen comprising the crystalline forms described herein. A crystalline form of endoxifen may provide the advantage of bioavailability and stability, suitable for use as an active ingredient in a pharmaceutical composition. Variations in the crystal structure of a pharmaceutical drug substance or active ingredient may affect the dissolution rate (which may affect bioavailability, etc.), manufacturability (e.g., ease of handling, ability to consistently prepare doses of known strength) and stability (e.g., thermal stability, shelf life, etc.) of a pharmaceutical drug product or active ingredient. Such variations may affect the preparation or formulation of pharmaceutical compositions in different dosage or delivery forms, such as solid oral dosage forms including tablets and capsules. Compared to other forms such as non-crystalline or amorphous forms, crystalline forms may provide desired or suitable hygroscopicity, particle size controls, dissolution rate, solubility, purity, physical and chemical stability, manufacturability, yield, and/or process control. Thus, crystalline forms of endoxifen may provide advantages such as: improving the manufacturing process of an active agent or the stability or storability of a drug product form of the compound or an active ingredient, and/or having suitable bioavailability and/or stability as an active agent.

[0168] The use of certain solvents and fractional crystallization methods has been found to produce different polymorphic forms of endoxifen, including any one or more of polymorphic Forms I, II

and II, which may exhibit one or more favorable characteristics described above. The processes for the preparation of the polymorphs described herein, and characterization of these polymorphs are described in greater detail below.

Formula III, Form I

[0169] In certain aspects, the present disclosure provides polymorphic Form I of a compound of Formula (III), wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer (i.e., (Z)-endoxifen). In some embodiments, polymorphic Form I exhibits an x-ray powder diffraction (XRPD) pattern substantially as shown in **Fig. 9** or **Fig. 10**. In some embodiments, polymorphic Form I has an XRPD pattern comprising at least two, at least three, at least four, at least five, or at least six of the major peaks as the XRPD pattern substantially as shown in **Fig. 9** or **Fig. 10**.

[0170] The term "substantially as shown in" when referring, for example, to an XRPD pattern, includes a pattern that is not necessarily identical to those depicted herein, but that falls within the limits of experimental error or deviations when considered by one of ordinary skill in the art. The relative intensities of XRPD peaks can vary, depending upon the particle size, the sample preparation technique, the sample mounting procedure and the particular instrument employed. Moreover, instrument variation and other factors can affect the two theta (2θ) values. Accordingly, when a specified two theta angle is provided, it is to be understood that the specified two theta angle can vary by the specified value ± 0.5°, such as ± 0.4°, ± 0.3°, ± 0.2°, or ± 0.1°. As used herein, "major peak" refers to an XRPD peak with a relative intensity greater than 30%, such as greater than 35%. Relative intensity is calculated as a ratio of the peak intensity of the peak of interest versus the peak intensity of the largest peak in the XRPD pattern.

[0171] In certain embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta. In some embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising peaks at 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3° two theta. In some embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, and at least one peak selected from 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3° two theta. In some embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising peaks at 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta. In some embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, and

at least one peak selected from 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta. In some embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, and at least one peak selected from 12.3 ± 0.3°, 16.0 ± 0.3°, 18.8 ± 0.3°, 26.5 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta. In some embodiments, polymorphic Form I is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta, and peaks at 12.3 ± 0.3°, 16.0 ± 0.3°, 18.8 ± 0.3°, 26.5 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.

[0172] In certain embodiments, the present disclosure provides a composition comprising polymorphic Form I. Greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition may be polymorphic Form I. In some embodiments, the composition comprises 0.01 mg to 200 mg of polymorphic Form I. In some embodiments, the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of polymorphic Form I.

Formula III, Form II

[0173] In certain aspects, the present disclosure provides polymorphic Form II of a compound of Formula (III), wherein the composition comprises the (E)-isomer and the (Z)-isomer of the compound of Formula (III) (i.e., (E)-endoxifen and (Z)-endoxifen) in an E/Z ratio between 0.9 and 1.3, such as about 1.1. In some embodiments, polymorphic Form II exhibits an x-ray powder diffraction (XRPD) pattern substantially as shown in **Fig. 11** or **Fig. 12**. In some embodiments, polymorphic Form II has an XRPD pattern comprising at least two, at least three, at least four, at least five, or at least six of the major peaks as the XRPD pattern substantially as shown in **Fig. 11** or **Fig. 12**.

[0174] In certain embodiments, polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta. In some embodiments, polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising a peak at 22.0 ± 0.3° two theta. In some embodiments, polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta and a peak at 22.0 ± 0.3° two theta. In some embodiments, polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising at least one peak selected from 6.6 ± 0.3°, 13.3 ± 0.3° and 20.0 ± 0.3° two theta. In some embodiments, polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta, and at least one peak selected from 6.6 ± 0.3°, 13.3 ± 0.3° and 20.0 ± 0.3° two theta. In some embodiments,

polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta, and at least one peak selected from 6.6 ± 0.3°, 13.3 ± 0.3°, 20.0 ± 0.3° and 22.0 ± 0.3° two theta. In some embodiments, polymorphic Form II is characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta, and peaks at 6.6 ± 0.3°, 13.3 ± 0.3°, 20.0 ± 0.3° and 22.0 ± 0.3° two theta.

[0175] In certain embodiments, the present disclosure provides a composition comprising polymorphic Form II. Greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition may be polymorphic Form II. In some embodiments, the composition comprises 0.01 mg to 200 mg of polymorphic Form II. In some embodiments, the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of polymorphic Form II.

Formula III, Form III

[0176] In certain aspects, the present disclosure provides polymorphic Form III of a compound of Formula (III), wherein the composition comprises the (E)-isomer and the (Z)-isomer of the compound of Formula (III) (i.e., (E)-endoxifen and (Z)-endoxifen) in an E/Z ratio between 0.9 and 1.3, such as about 1.1. In some embodiments, polymorphic Form III exhibits an x-ray powder diffraction (XRPD) pattern substantially as shown in **Fig. 13**. In some embodiments, polymorphic Form III has an XRPD pattern comprising at least two, at least three, at least four, at least five, or at least six of the major peaks as the XRPD pattern substantially as shown in **Fig. 13**.

[0177] In certain embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta. In some embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising a peak at 25.3 ± 0.3° two theta. In some embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta and a peak at 25.3 ± 0.3° two theta. In some embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising at least one peak selected from 18.2 ± 0.3°, 22.5 ± 0.3° and 26.8 ± 0.3° two theta. In some embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta, and at least one peak selected from 18.2 ± 0.3°, 22.5 ± 0.3° and 26.8 ± 0.3° two theta. In some embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta, and at

least one peak selected from 18.2 ± 0.3°, 22.5 ± 0.3°, 25.3 ± 0.3° and 26.8 ± 0.3° two theta. In some embodiments, polymorphic Form III is characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta, and peaks at 18.2 ± 0.3°, 22.5 ± 0.3°, 25.3 ± 0.3° and 26.8 ± 0.3° two theta.

[0178] In certain embodiments, the present disclosure provides a composition comprising polymorphic Form III. Greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition may be polymorphic Form III. In some embodiments, the composition comprises 0.01 mg to 200 mg of polymorphic Form III. In some embodiments, the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of polymorphic Form III.

Endoxifen Free Base Compositions

[0179] In one aspect, the present disclosure provides stable (Z)-endoxifen free base or salts thereof, and compositions comprising (Z)-endoxifen free base or salts thereof. In some embodiments, the pharmaceutical composition comprises endoxifen predominantly as (Z)-endoxifen free base.

[0180] In certain embodiments, compositions may comprise endoxifen as at least 0.1%, at least 0.2%, at least 0.3%, at least 0.4%, at least 0.5%, at least 1%, at least 5%, at least 10%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, at least 99.99%, or 100% of (Z)-endoxifen free base wt/wt of total endoxifen in the composition. In at least one composition, the composition comprises ≥90% of (Z)-endoxifen free base wt/wt of the total endoxifen in the composition. In another embodiment, the composition comprises ≥95% of (Z)-endoxifen free base wt/wt of the total endoxifen in the composition. In yet another embodiment, the compositions comprise ≥96%, ≥97%, ≥98%, ≥99%, or ≥99.5% of (Z)-endoxifen free base wt/wt of the total endoxifen in the composition.

[0181] In other embodiments, compositions comprising endoxifen comprise 0.01% to 20%, 0.05% to 15%, or 0.1% to 10% of (Z)-endoxifen wt/wt or w/v of the composition. In at least one embodiment, the compositions comprising endoxifen comprise 0.01% to 20% of (Z)-endoxifen wt/wt or w/v of the composition. In various other embodiments, the compositions comprising endoxifen comprise 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0,09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 2%, 3%, 4%, 5%, 10%, or 20% of (Z)-endoxifen wt/wt of the composition.

[0182] In an aspect, the compositions comprising (Z)-endoxifen further comprise (E)-endoxifen. In some embodiments, the endoxifen in the composition has a ratio of (E)-endoxifen to (Z)-endoxifen

(E/Z-ratio) of 1:99; 5:95; 10:90, 15:85; 20:80, 25:75; 30:70; 40:70, 45:55; 50:50; 55:45; 60:40; 65:45; and 70:30. In other embodiments, compositions comprise endoxifen having E/Z-ratio ranging from 10:90 to 70:30. In still other embodiments, compositions comprise endoxifen having E/Z-ratio ranging from 45:55 to 55:45.

[0183] Unless specifically referred to by the prefix (Z), (E) or (E/Z), endoxifen used generally without a prefix is used herein to include to any or all endoxifen isoforms.

Endoxifen Salt Compositions

[0184] In some embodiments, the present disclosure provides compositions comprising salts of endoxifen. In some embodiments, the present disclosure provides compositions comprising pharmaceutically acceptable salts of endoxifen. Provided herein in certain embodiments are compositions comprising 1%, 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.99% or 100% of endoxifen salt.

[0185] In some embodiments, the salt is selected from the group consisting of arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, Teoclate, triethiodide, benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc. In some embodiments, the salt is endoxifen gluconate. Endoxifen gluconate can be selected from the group consisting of (Z)-endoxifen D-gluconate, (E)-endoxifen D-gluconate, (Z)-endoxifen L-gluconate, (E)-endoxifen L-gluconate or a combination thereof.

[0186] In some embodiments, a composition comprising endoxifen gluconate is comprised of 10% to 100% of (Z)-endoxifen D-gluconate on a wt/wt basis of total endoxifen gluconate in the composition. In some embodiments, a composition comprising endoxifen gluconate is comprised of 10% to 100% of (Z)-endoxifen L-gluconate on a wt/wt basis of total endoxifen in the composition.

[0187] In other embodiments, a composition comprising endoxifen gluconate is comprised of 10%, 20%, 30%, 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.75%, 99.99%, or 100% of (Z)-endoxifen D-gluconate or (Z)-endoxifen L-gluconate with respect to total endoxifen gluconate. In some embodiments, the compositions comprise at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least

94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, or at least 99.99% of (Z)-endoxifen D-gluconate, (Z)-endoxifen L-gluconate or a combination thereof.

[0188] Provided herein in some embodiments are compositions comprising (Z)-endoxifen D-gluconate and (E)-endoxifen D-gluconate. (Z)-endoxifen D-gluconate and (E)-endoxifen D-gluconate may be present in the compositions at ratios ranging from 10:90 to 99:1 wt/wt or v/v respectively. In some embodiments, the ratio of (Z)-endoxifen D-gluconate to (E)-endoxifen D-gluconate is (wt/wt or v/v) 10:90 to 99:1 (e.g., 45:55, 50:50, 60:40, 70:30, 80: 20, 90:10; 91:9; 92:8; 93:7; 94:8; 95:5, 96:4, 97:3, 98:2, 99:1, 99.5:0.5, or 99.99:0.01) respectively. In certain embodiments, the ratio of (Z)-endoxifen D-gluconate to (E)-endoxifen D-gluconate (wt/wt or v/v) is 90:10; 91:9; 92:8; 93:7; 94:8; 95:5, 96:4, 97:3, 98:2, 99:1, 99.5:0.5, or 99.99:0.01. One of skill in the art will recognize that other combinations of endoxifen gluconate isomers are encompassed in the present disclosure.

[0189] In some embodiments, a composition comprising endoxifen gluconate comprises 0.01%, 0.05%, 0.01%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% endoxifen gluconate (wt/wt) or (w/v) of the composition. In some embodiments, a composition comprising endoxifen gluconate comprises 0.01%, 0.05%, 0.01%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19% or 20% (Z)-endoxifen gluconate (wt/wt) or (w/v) of the composition.

[0190] The compounds and compositions of the present disclosure can be administered to a subject in need thereof by any route known in the art, including without limitation, oral, parenteral, topical, and intraductal delivery. Accordingly, compositions disclosed herein are formulated to be compatible with the intended route of administration.

[0191] In some embodiments, the compositions comprising endoxifen further comprise an excipient. Such an excipient can be compatible with the intended route of administration.

Endoxifen Polymorph Compositions

[0192] In one aspect, the present disclosure provides compositions comprising one or more polymorphic forms, such as Form I, Form II, or Form II described herein, of endoxifen. In some embodiments, the pharmaceutical composition comprises endoxifen predominantly as polymorph Form I. In some embodiments, the pharmaceutical composition comprises endoxifen predominantly as polymorph Form II. In some embodiments, the pharmaceutical composition comprises endoxifen predominantly as polymorph Form III.

[0193] In certain embodiments, a composition comprises endoxifen as at least 0.1%, at least 0.2%, at least 0.3%, at least 0.4%, at least 0.5%, at least 1%, at least 5%, at least 10%, at least 20%, at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, at least 99.5%, at least 99.99%, or 100% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt of total endoxifen in the composition. In at least one composition, the composition comprises ≥90% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt of the total endoxifen in the composition. In another embodiment, the composition comprises ≥95% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt of the total endoxifen in the composition. In yet another embodiment, the composition comprises ≥96%, ≥97%, ≥98%, ≥99%, or ≥99.5% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt of the total endoxifen in the composition. When a particular percentage by weight of endoxifen is a single polymorphic form, the remainder of endoxifen in the composition is some combination of amorphous endoxifen and/or one or more polymorphic forms of endoxifen excluding the single polymorphic form. When the polymorphic endoxifen is defined as one particular form of endoxifen, the remainder is made up of amorphous endoxifen and/or one or more polymorphic forms other than the particular form specified. Examples of single polymorphic forms include Forms I, II and III of endoxifen, as well as descriptions of a single polymorphic form characterized by one or more properties as described herein.

[0194] In other embodiments, a composition comprising endoxifen comprises 0.01% to 20%, 0.05% to 15%, or 0.1% to 10% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt or w/v of the composition. In at least one embodiment, the composition comprising endoxifen comprises 0.01% to 20% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt or w/v of the composition. In various other embodiments, the composition comprising endoxifen comprises 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0,09%, 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6%, 0.7%, 0.8%, 0.9%, 1%, 2%, 3%, 4%, 5%, 10%, or 20% of a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, wt/wt of the composition. In an aspect, a composition comprising a single polymorphic Form of endoxifen, such as Form I, Form II, or Form III, further comprises a second polymorphic Form of endoxifen.

Oral Formulations

[0195] In some embodiments, a pharmaceutical composition of the present disclosure is formulated for oral delivery. Compositions intended for oral use may be prepared in solid or fluid unit dosage forms. In at least some embodiments, the compositions are formulated for oral delivery as tablets, caplets, capsules, pills, powders, troches, elixirs, suspensions, syrups, wafers, chewing gums, dragees, lozenges, and the like.

[0196] In some embodiments, the oral dosage forms are solid oral dosage forms such as tablets, caplets, and capsules. In some embodiments, the capsule is a hard capsule or a soft capsule. In other embodiments, the capsule is a gelatin capsule, gelatin-free capsule, a "cap-in-cap" capsule, alginate capsule, hydroxypropylmethyl cellulose (HPMC) capsule, a polyvinyl alcohol (PVA) capsule, a hypromellose capsule, or a starch capsule.

Excipients

[0197] In some embodiments, an oral composition comprising (Z)-endoxifen or a salt thereof further comprises one or more excipients. In some embodiments, an oral composition comprising endoxifen or a polymorph thereof further comprises one or more excipients. Accordingly, compositions designed for oral administration can be made with an inert or active excipient or with an edible carrier as disclosed herein.

[0198] In various embodiments, the composition provided herein comprises from about 1% to about 99.99%, about 5% to about 95%, about 5% to about 90%, about 10% to about 80%, about 15% to about 70%, about 20% to about 60%, from about 30% to about 95%, from about 50% to about 90%, from about 60% to about 90%, from about 60% to about 80%, or from about 70% to about 80% by weight of one or more excipients. In certain embodiments, the composition provided herein comprises about 99.99%, about 95%, about 90%, about 85%, about 80%, about 75%, about 70%, about 65%, about 60%, about 55%, or about 50% by weight of one or more excipients. In certain embodiments, the composition provided herein comprises about 99.99%, about 99%, about 98%, about 97%, about 96%, about 95%, about 94%, about 93%, about 92%, about 91%, about 90%, about 89%, about 88%, about 87%, about 86%, or about 85% by weight of one or more excipients. In certain embodiments, the composition provided herein comprises about 85%, about 84%, about 83%, about 82%, about 80%, about 79%, about 78%, about 77%, about 76%, about 75%, about 74%, about 73%, about 72%, about 71%, about 70%, about 69%, about 68%, about 67%, about 66%, or about 65% by weight of one or more excipients. In certain embodiments, the composition provided herein comprises about 55%, about 54%, about 53%, about 52%, about 51%, about 50%,

about 49%, about 48%, about 47%, about 46%, or about 45% by weight of one or more excipients. In certain embodiments, the composition provided herein comprises about 30%, about 29%, about 28%, about 27%, about 26%, about 25%, about 24%, about 23%, about 22%, about 21%, or about 20% by weight of one or more excipients.

[0199] Examples of excipients that can be used in the compositions formulated for oral administration are provided herein and can include, but are not limited to, one or more of bulking agents, binders, fillers, disintegrating agents, lubricants, glidants, control release agents, enteric coatings, film-forming agents, plasticizers, colorants, sweetners, flavoring agents and the like, or any combination thereof.

[0200] Binders suitable for use in the pharmaceutical compositions provided herein include, but are not limited to, sucrose, starches such as corn starch, potato starch, or starches such as starch paste, pregelatinized starch, and starch 1500, PEG 6000, methocel, walocel HM, Luvitec, Luvicaparolactam, Avicel, SMCC, UNIPURE, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, tragacanth, guar gum, cellulose and its derivatives (e.g., ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone, methyl cellulose, polyvinyl pyrrolidone, hydroxypropyl methyl cellulose, (e.g., Nos. 2208, 2906, 2910), microcrystalline cellulose, and mixtures thereof. Suitable forms of microcrystalline cellulose include, but are not limited to, the materials sold as AVICEL PH 101, AVICEL PH 103 AVICEL RC 581, AVICEL PH 105 (available from FMC Corporation, American Viscose Division, Avicel Sales, Marcus Hook, Pa.), and mixtures thereof. In some embodiments, the binder is a mixture of microcrystalline cellulose and sodium carboxymethyl cellulose. Suitable anhydrous or low moisture excipients or additives include AVICEL PH 103 and Starch 1500 LM.

[0201] Examples of fillers suitable for use in the pharmaceutical compositions provided herein include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), sugars such as dextrose, sucrose, lactose, a salt such as calcium carbonate, calcium phosphate, sodium carbonate, sodium phosphate, starches, microcrystalline cellulose, powdered cellulose, cellulosic bases such as methyl cellulose, carboxymethyl cellulose dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pregelatinized starch, and mixtures thereof.

[0202] One or more binder or filler in compositions is typically present in from about 10% to about 99% (wt/wt) of the composition or the dosage form. In some embodiments, binders and/or fillers in a composition comprise about 15% to 99%, about 20% to 60%, about 25% to 55%, about 30% to 50%, about 35% to 60%, about 50% to 99% (wt/wt) of the composition.

[0203] Disintegrants can be used in the compositions to provide tablets that disintegrate when exposed to an aqueous environment. Tablets that contain too much disintegrant may disintegrate in storage, while those that contain too little may not disintegrate at a desired rate or under the desired conditions. Thus, a sufficient amount of disintegrant that is neither too much nor too little to detrimentally alter the release of the active ingredients should be used to form solid oral dosage forms. In some embodiments, the disintegrant is deep in the oral solid dosage form to delay disintegration. The amount of disintegrant used varies based upon the type of formulation, and is readily discernible to those of ordinary skill in the art.

[0204] Typical compositions comprise from 0.5% to 15% (wt/wt) of disintegrant. In some embodiments, compositions comprise from 1% to 5% (wt/wt) of disintegrant in the composition. In another embodiment, the disintegrant is 1% to 25%, 2% to 20%, 5% to 15%, 8% to 12%, or about 10% (wt/wt) of the composition.

[0205] Disintegrants that can be used in the pharmaceutical compositions provided herein include, but are not limited to, agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and mixtures thereof.

[0206] Lubricants that can be used in the pharmaceutical compositions provided herein include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, magnesium stearate or potassium stearate, ethyl oleate, ethyl laureate, agar, and mixtures thereof. Additional lubricants include, for example, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Tex.), CAB O SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.), Q7-9120 (Dow Corning), and mixtures thereof. If used at all, lubricants are typically used in an amount of less than 1% (wt/wt) of the compositions or dosage forms into which they are incorporated. In yet another embodiment, the lubricant is 0.1% to 3%, such as 0.5% to 1% (wt/wt), of the composition.

[0207] Plasticizers may be added to control the softness or pliability of oral dosage forms such as shell of a capsule, caplet or a tablet and thus, may improve the mechanical properties of the pH-sensitive materials of the coatings on the oral dosage forms. Suitable plasticizers, include, without limitation, petroleum oils (for e.g., a paraffinic process oil, a naphthenic process oil, and an aromatic

process oil), squalene, squalane, plant oils, (e.g., olive oil, camelia oil, castor oil, tall oil, and a peanut oil), silicon oils, dibasic acid esters, (e.g., dibutyl phthalate, and dioctyl phthalate), liquid rubbers (e.g., polybutene and a liquid isoprene rubber), liquid fatty acid esters (e.g., isopropyl myristate ISM), hexyl laurate, diethyl sebacate, and diisopropyl sebacate, triethyl citrate, triacetin, diethylene glycol, polyethylene glycols, polypropylene glycol, phthalates, sorbitol, glycol salicylate, crotaminton, and glycerin or mixtures thereof. The amount of plasticizer may vary depending upon the chemical composition of the pharmaceutical preparation. In one embodiment, the at least one plasticizer is sorbitol, dimethyl isosorbide, or a glycerol. In another embodiment, the plasticizer is 1% to 10%, such as 3% to 5% (wt/wt), of the composition.

[0208] Examples of glidants include, but are not limited to, colloidal silicone dioxide, cellulose, calcium phosphate, di or tri-basic and the like.

[0209] As an example of sweetners or sweetening agents include sucrose, saccharin, dextrose, maltose, sugar substitutes, aspartame, xylitol, mannitol, cyclamate, sucralose, maltitol, sorbitol, acesulfame K and the like.

[0210] Examples of flavoring agents include peppermint, methyl salicylate, peppermint, spearment, methyl salicylate, raspberry, red berry, strawberry, pineapple, orange, cherry and the like.

[0211] Compositions formulated for oral delivery as disclosed herein, for example, tablets, caplets, and capsules, may be coated with one or more enteric coating agent, control release agent or film forming agent to control or delay disintegration and absorption of the compositions comprising endoxifen or salts thereof in the gastrointestinal tract and thereby provide a sustained action over a longer period of time. Accordingly, in some embodiments, the tablet can be an enteric tablet, the caplet can be an enteric caplet, or the capsule can be an enteric capsule. The enteric tablets, enteric caplets, or enteric capsules of the present disclosure may be prepared by techniques known in the art.

[0212] Pharmaceutical preparations disclosed herein may comprise a control release agent. Examples of control release agent suitable for use include, without limitation, pH-dependent polymers, acid-insoluble polymers, methyl acrylate-methacrylic acid copolymers, cellulose acetate phthalate (CAP), cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate (hypromellose acetate succinate), polyvinyl acetate phthalate (PVAP), methyl methacrylate-methacrylic acid copolymers, shellac, cellulose acetate trimellitate, sodium alginate, zein, waxes, including synthetic waxes, microcrystalline waxes, paraffin wax, carnauba wax, and beeswax; polyethoxylated castor oil derivatives, hydrogenated oils, glyceryl mono-, di- tribenates, glyceryl monostearate, glyceryl distearate, long chain alcohols, such

as stearyl alcohol, cetyl alcohol, and polyethylene glycol; and mixtures thereof. In some embodiments, a time delay material such as glyceryl monostearate or glyceryl distearate may be used. In other embodiments, the controlled release reagent is a digestible waxy substance such as hard paraffin wax.

[0213] In some embodiments, compositions may comprise one or more of pH-dependent polymers such as acid insoluble polymers. The pH-dependent polymers become increasingly permeable above pH 5.0 but are impermeable at pH below 5.0 whereas acid insoluble polymers become soluble in neutral to weakly alkaline conditions. Such control release polymers target upper small intestines and colon. Non-limiting examples of acid-insoluble polymers include cellulose acetate phthalate, cellulose acetate butyrate, hydroxypropyl methyl cellulose phthalate, algenic acid salts such as sodium or potassium alginate, shellac, pectin, acrylic acid-methylacrylic acid copolymers (commercially available under the tradename EUDRAGIT® L and EUDRAGIT® S from Rohm America Inc., Piscataway, NJ as a powder or a 30% aqueous dispersion; or under the tradename EASTACRYL®, from Eastman Chemical Co., Kingsport, TN, as a 30% dispersion). Additional examples include EUDRAGIT® L100-55, EUDRAGIT® L30D-55, EUDRAGIT® L100, EUDRAGIT® L100 12,5, EUDRAGIT® S100, EUDRAGIT® S12,5, EUDRAGIT® FS 30D, EUDRAGIT® E100, EUDRAGIT® E 12,5, and EUDRAGIT® PO. In at least one embodiment, the composition comprises EUDRAGIT® L100-55. EUDRAGIT® RS and RL and EUDRAGIT®NE and NM are also useful polymers for the purpose of this disclosure. In some embodiments, the composition comprises EUDRAGIT ® L30D 55. In another embodiment, the preparation comprises EUDRAGIT® FS 30D. One of skill in the art will recognize that at least some acid insoluble polymers listed herein will also be biodegradable.

[0214] For time delay or delayed-release pharmaceutical preparations of oral dosage forms, glyceryl monostearate, glyceryl distearate, and acid-insoluble polymers, for example polymethacrylate pH-sensitive polymer-based coatings can be used, (e.g., as coating material, i.e., enteric coating agents, for enteric coating of capsules, caplets, and tablets). Commercial sources for delayed-release oral dosage forms are available, for example DRCaps made of hypromellose (HPMC) from Capsugel, USA. Such delayed-release oral dosage forms forms are acid-resistant and can resist acidity as seen in stomach for at least 30 min, such as for at least 1 hour, for at least 1.5 hour, or for at least 2 hours. Such delayed release oral dosage forms can release at least 40%, at least 50%, at least 60%, at least 70%, at least 80% or at least 90% of the endoxifen or salts thereof in the intestines (small intestines, large intestine/colon etc).

[0215] In an aspect of the present disclosure, the enteric tablets, enteric caplets, and enteric capsules may be uncoated. Hard uncoated capsules with enteric capability using intrinsically enteric capsule technology (for example, EnTrinsic Drug Delivery available from Capsugel) are suitable for the purpose of the present disclosure.

[0216] In various embodiments, the enteric tablet is a hard tablet made with free-flowing powder of (Z)-endoxifen or a salt thereof. In various embodiments, the enteric capsule is a capsule made with free-flowing powder of (Z)-endoxifen or a salt thereof. In various embodiments, the enteric tablet is a hard tablet made with free-flowing powder of endoxifen or a polymorph thereof. In various embodiments, the enteric capsule is a capsule made with free-flowing powder of endoxifen or a polymorph thereof.

[0217] In some embodiments, the enteric capsule is a non-animal based capsule, such as a hypromellose capsule (for example, commercially available self-gelling Vcaps, VCaps Plus, VCaps enteric, other enteric capsules made using Xcellodose, ENCODE colonic delivery technology, and EnTrinsic™ drug delivery technology from Capsugel). Other technologies known in the art and available commercially (for example, Qualicaps, USA, Nutrascience, USA, etc.) for the formulating enteric forms of oral solid dosage forms can also be utilized. In at least one embodiment, the capsule is an API-in-capsule, meaning that the (Z)-endoxifen free base or salts thereof is filled neat into the capsule. In such API-in-capsule oral dosage forms, the active ingredient, (Z)-endoxifen or salts thereof can be free flowing powders or micronized powders. When the dosage form is a capsule, in at least one embodiment, the capsule can be a seamless capsule or a banded capsule.

[0218] Rapid absorption and bioavailability of the anti-cancer therapeutics such as endoxifen that can further reduce the cancer growth rate are highly desirable. In an aspect, the present disclosure provides that the compositions are formulated for certain pharmacokinetic (PK) properties.

[0219] In one aspect, rapid achievement of maximal and steady state plasma levels of endoxifen is a particular aspect of the present disclosure. The present disclosure provides compositions that achieve a maximal plasma level of endoxifen ranging within 2 to 30 hours, within 3 to 20 hours, within 2 to 10 hours or within 4 to 8 hours after administration of the compositions. Accordingly, in some embodiments, time to maximal (peak) plasma level of endoxifen ranges from 2 to 10 hours after administration of the composition. In some embodiments, the time to maximal plasma level of endoxifen ranges from 4 to 8 hours after administration of a composition disclosed herein.

[0220] Rapid achievement of steady-state plasma levels of endoxifen is also highly desirable, and a composition of the present disclosure may provide a plasma level of endoxifen in a subject administered the composition comprising a polymorphic form of endoxifen, (Z)-endoxifen or a salt

thereof that rapidly achieves steady state. Steady state plasma levels can be achieved from day 7 to day 21. In some embodiments, the steady state plasma levels can be achieved by day 7 (Figure 5) upon daily administration of a composition disclosed herein.

[0221] In an aspect, the present disclosure provides that circulating endoxifen released from a composition disclosed herein can be cleared faster than tamoxifen. Terminal elimination half life of tamoxifen is said to be 5-7 days (Jordan C. Steroids. 2007 Nov; 72(13): 829–842) and peak concentration time of tamoxifen is approximately 5 hours post-dose. Endoxifen released from a composition disclosed herein can have a terminal elimination half-life ranging from 30 to 60 hours, significantly lower than tamoxifen. In some embodiments, the mean half -life ranges from 40 to 53 hours. The mean ratio of AUC_{24hr} (Day 21)/$AUC_{0\text{-}inf}$ (Day1) typically ranges from 0.7 to 1.2 for compositions comprising 1 mg to 4 mg (Z)-endoxifen, or a salt thereof. Thus, accumulation of endoxifen released from a compositions disclosed herein does not significantly vary over continued treatment.

[0222] In another aspect, a composition described herein achieves absorption of endoxifen that is therapeutically effective.

[0223] Area under Curve $AUC_{(0\text{-}24hr)}$ ("AUC_{24hr}") describes the total exposure of the subject to a drug from time of dosing (0 hr) over a 24 hour period. Compositions comprising (Z)-endoxifen or a salt thereof typically achieve mean (AUC_{24hr}) of 150 hr*ng/mL to 600 hr*ng/mL on Day 1 of initial (first) dose of a composition comprising 1 mg to 4 mg of (Z)-endoxifen. Compositions comprising (Z)-endoxifen or a salt thereof typically achieve mean AUC_{24hr} of 400 hr*ng/mL to 2500 hr*ng/mL on Day 21 of initial (first) dose of compositions comprising 1 mg to 4 mg of (Z)-endoxifen.

[0224] $AUC_{0\text{-}inf}$ ("$AUC_{0\text{-}inf}$"), a time-averaged concentration of drug circulating in the body fluid analyzed (normally plasma, blood or serum), describes the total exposure of the subject to a drug. The present disclosure provides that the exposure of a subject to endoxifen ($AUC_{0\text{-}inf}$) can be dose proportional. In some embodiments, $AUC_{0\text{-}inf}$ ranges from 200 hr*ng/mL to 10000 hr*ng/mL. In other embodiments, the $AUC_{0\text{-}inf}$ ranges from 300 hr*ng/mL to 8000 hr*ng/mL. In certain embodiments, the $AUC_{0\text{-}inf}$ ranges from 400 hr*ng/mL to 6000 hr*ng/mL over the dosing range of 1 mg to 4 mg of (Z)-endoxifen (for example, see **Table 17**).

[0225] Dissolution of the oral dosage forms disclosed herein is tested by the dissolution tests according to the current methods of USP 711. In some embodiments, the oral dosage forms disclosed herein are protected from the acidic environment of the stomach and do not dissolve for at least 2 hours, at least 3 hours, at least 4 hours, at least 5 hours, 6 hours, at least 7 hours or at least 8 hours. In at least one embodiment, the oral dosage forms do not release endoxifen for at least 6

hours. In another embodiment, the oral dosage forms do not release endoxifen or a salt thereof for at least 2 hours.

[0226] In other embodiments, less than 10% of (Z)-endoxifen in a composition comprising endoxifen or a salt thereof disclosed herein is released in the stomach ater 2 hours after administration; or wherein less than 40% of (Z)-endoxifen is released in the stomach after 4 hours of administration; or less than 50% of (Z)-endoxifen is released in the stomach after 6 hours of administration, as tested by a method of USP 711.

[0227] In another embodiment, a composition disclosed herein releases in the stomach less than 10% of (Z)-endoxifen in 2 hours after administration, less than 40% of (Z)-endoxifen in 4 hours after administration; and less than 50% of (Z)-endoxifen in 6 hours after administration, as tested by a method of USP 711.

[0228] In yet another embodiment, the composition is formulated to release in the small intestine, such that at least 10% of endoxifen is released after 4 hours after administration; or at least 30% of endoxifen is released after 6 hours after administration; or at least 40% of endoxifen is released after 7 hours after administration; or at least 50% of endoxifen is released after 8 hours after administration, as tested by a method of USP 711.

[0229] In a further embodiment, as determined by a method of USP 711, the composition is formulated to release in the colon at least 50% of endoxifen after 8 hours after administration.

[0230] In still further embodiments, the composition is formulated to release in the colon at least 20% of endoxifen after 4 hours after administration; at least 40% of endoxifen after 6 hours after administration; at least 60% of endoxifen after 7 hours after administration; or at least 80% of endoxifen after 8 hours after administration.

[0231] An oral dosage form can be of any shape suitable for oral administration, such as spherical (0.05 - 5 mL), oval (0.05 - 7 mL), ellipsoidal, pear (0.3 - 5 mL), cylindrical, cubic, regular and/or irregular shaped. An oral dosage form may be of any size suitable for oral administration, for example, size 0, size 2, and the like.

[0232] One of skill in the art will further recognize that compositions disclosed herein may comprise one or more of the excipients known in the art and disclosed herein in any combination appropriate for a desired formulation or preparation. Additional excipients may generally be found in Remington's The Science and Practice of Pharmacy, Meade Publishing Co., United States Pharmacopeia/National Formulary. One of skill in the art will be able to select suitable excipients necessary for the preparation of the formulations and appropriate dosage forms compatible with the route of administration based on his or her skill and knowledge in the art and the disclosures made

herein. In all cases, the ultimate dosage form should be sterile and stable under the conditions of manufacture and storage.

[0233] For formulations of the solid dosage compositions disclosed herein, as the water activity (A_w) is less than 0.75, testing Total Aerobic Plate Count (TAC) and USP indicator organism is typically not necessary. The publication, "Microbial Bioburden on Oral Solid Dosage Form," by Jose E. Martinez, Pharmaceutical Technology, February 2002, pages 58 to 70, is hereby incorporated by reference in its entirety.

[0234] Furthermore, since formulations of the compositions disclosed herein also have water activity of less than 0.75, then detailed microbial testing is typically not necessary. TAC is an estimation of the total viable aerobic microbes present in a sample of raw material, in-process material, or finished product. Samples are analyzed in accordance with the most current USP 39 <61>, "Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests."

[0235] Acceptable TAC for oral solid dosage forms (OSDFs) are established for the formulation of the inventive compositions in terms of alert and action levels, which could be 1000 cfu g/mL, and 10,000 cfu g/mL, respectively. A TAC that is 20,000 cfu g/mL may be considered unacceptable.

[0236] For other formulations, such as liquid or fluid formulations with water activity of less than 0.75, Tests for Specified Microorganisms (*S. aureus*, *Ps. aeruginosa*, Salmonella, *C. albicans*, Clostridia, *E. coli* and Bile Tolerant Gram negative bacteria) in compliance with USP Guidelines Chapter 62 may not need to be performed.

Methods of Use

[0237] Compounds of Formulae (I), (II), (III), and (IV), endoxifen salts disclosed herein, polymorphic forms of endoxifen disclosed herein, and compositions comprising them may be used in the manufacture of medicaments for use in the treatment of a subject in need thereof, for example, subjects having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

[0238] The compositions of the present disclosure may be used as a primary therapy, as a part of a neo-adjuvant therapy (to primary therapy), or as part of adjuvant therapy regimen, where the intention is to ameliorate or cure a subject having or at risk of having a hormone-dependent breast disorder, hormone-dependent reproductive tract disorder, or both.

[0239] In certain embodiments, the disorder is a hormone-dependent breast disorder. In other embodiments, the disorder is hormone-dependent reproductive tract disorder. In still other embodiments, the subject has both a hormone-dependent breast disorder and a hormone-dependent

reproductive tract disorder. In some embodiments, the hormone dependent disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer or vulvar cancer.

[0240] In some embodiments, the breast disorder is increased breast density. For example, the breast disorder is a class B (formerly Class II), class C (formerly class III) or class D (formerly class IV) breast density.

[0241] In some embodiments, the hormone-dependent breast disorder or hormone-dependent reproductive tract disorder is precocious puberty. In other embodiments, the hormone-dependent breast disorder or hormone-dependent reproductive tract disorder is McCune-Albright Syndrome.

[0242] In some embodiments, the breast disorder is gynecomastia. In some embodiments, gynecomastia is presented secondarily to an underlying disease. Accordingly in some embodiments, the subject also has underlying disease selected from the group consisting of prostate cancer, cirrhosis and liver disease, male hypogonadism, hyperthyroidism, renal failure and in patients undergoing hemodialysis, or type I diabetes mellitis. In certain embodiments, the subject has prostate cancer as the underlying disease, wherein the subject has or is at risk of having gynecomastia.

[0243] In certain embodiments, the breast cancer is DCIS, LCIS, ILC, IDC, MIC, inflammatory breast cancer, ER-positive (ER+) breast cancer, HER2+ breast cancer, adenoid cystic (adenocystic) carcinoma, low-grade adenosquamatous carcinoma, medullary carcinoma, mucinous (or colloid) carcinoma, papillary carcinoma, tubular carcinoma, metaplastic carcinoma, or micropapillary carcinoma. In at least one embodiment, a single breast cancer tumor may be a combination of the foregoing or be a mixture of invasive and in situ cancer.

[0244] The present disclosure contemplates the use of the compounds and compositions disclosed herein at various stages in tumor development and progression, including the treatment of advanced and/or aggressive neoplasms, i.e., overt disease in a subject that is not amenable to cure by local modalities of treatment such as surgery or radiotherapy, metastatic disease, or locally advanced disease. Accordingly in some embodiments, the breast cancer is a pre-cancer, an early stage cancer, a non-metastatic cancer, a pre-metastatic cancer, or a locally advanced cancer. In at least one embodiment, the breast disorder is metastatic cancer. In some embodiments, the subject further has prostate cancer.

[0245] Current choice for therapeutics for such disorders remains tamoxifen, despite serious adverse effects, poor patient compliance and resistance to the drug due to low plasma endoxifen levels seen

subjects. Such subjects may have low endoxifen levels upon dosing with tamoxifen for any number of reasons, such as having CYP gene mutations, for example, in CYP2D6, CYP3A4, or CYP2C9, making them unable to metabolize tamoxifen to its active metabolite, endoxifen, or low or dysfunctional estrogen receptor preventing (or decreasing) sufficient tamoxifen uptake, for other reasons yet to be identified. Reported therapeutic levels of plasma tamoxifen in subjects dosed with 20 mg of oral tamoxifen is ≥ 30 nM ((Lyon et al. Genet Med. 2012 Dec;14(12):990-1000). Notwithstanding the mechanism underlying the low plasma endoxifen in a subject, the compositions of the present disclosure are useful for any condition wherein a subject has low endoxifen or the subject has or is at a risk of having hormone-dependent breast disorder or hormone-dependent reproductive tract disorder. Therefore, the compositions of the present disclosure can be particularly important in the treatment of tamoxifen-resistant, hormone-dependent breast disorders or hormone-dependent reproductive tract disorders.

[0246] Provided herein in certain embodiments are patient populations for whom the pharmaceutical compositions are particularly useful. The compositions of the present disclosure are also particularly important in the treatment of tamoxifen-refractory subjects with hormone-dependent breast disorders or hormone-dependent reproductive tract disorders. Accordingly, in some embodiments, the compositions disclosed herein are useful for the treatment of tamoxifen refractory or tamoxifen resistant subjects having or at risk of having hormone-dependent breast disorders, hormone-dependent reproductive tract disorders, or both. In some embodiments, compositions comprising an endoxifen salt, such as endoxifen gluconate, administered to such subject at the doses disclosed herein, will be advantageous.

[0247] Further, Donneyong et al. have shown that drug interactions between tamoxifen and selective serotonin reuptake inhibitors (SSRI) drugs like Prozac and Paxil (paroxetine) exist and are detrimental to breast cancer subjects (Donneyong et al. BMJ 2016;354:i5014). The SSRI drugs reduce or stop liver metabolism of tamoxifen to endoxifen in subjects on SSRI drugs. Thus, provided herein in certain embodiments are patient populations being treated or to be treated with SSRI drugs that would be benefitted by treatment with compositions of the present disclosure.

[0248] Compositions disclosed herein administered orally maintain the subject's plasma endoxifen at steady state levels greater than 30 nM, for example, at levels ranging from 30 nM to 80 nM or at levels ranging from 30 nM to 300 nM. In some embodiments, the plasma steady state endoxifen levels are maintained at >40 nM. Maintenance of such a plasma endoxifen at steady state levels greater than 30 nM is advantageous in that the likelihood of recurrence (relapse) of hormone-dependent breast disorders or hormone-dependent reproductive tract disorders, particularly breast

cancer, at plasma endoxifen levels lower than 30 nM is reduced. It is particularly advantageous for subjects that are poor-metabolizers of tamoxifen (with plasma endoxifen levels lower than 16 nM), intermediate metabolizers of tamoxifen (with plasma endoxifen levels lower than 27 nM) to be dosed with a composition disclosed herein. It also advantageous for subjects being treated or to be treated with antidepressant drugs such as SSRI drugs such as citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), paroxetine (Paxil, Pexeva), sertraline (Zoloft), vilazodone (Viibryd) and the like, for example, a subject having or likely to have depression.

[0249] Whether a subject is tamoxifen-refractory may be determined by dosing a subject with an initial dosage of tamoxifen and determining the subject's plasma endoxifen steady state level. Plasma endoxifen steady state levels in a subject dosed with tamoxifen serves as a biomarker for the tamoxifen-refractory subjects. The plasma endoxifen levels (acute and/or steady state) may be determined by obtaining from the subject a test sample, which may be blood sample, collected from the subject after dosing the subject with tamoxifen. Plasma or serum may be obtained from blood samples for testing the biomarker endoxifen levels. The initial dosage may comprise administering tamoxifen daily for at least 1 day, 2 days, 3 days, 15 days, 1 week, 2 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months. The subject may also be administered with a first composition comprising tamoxifen daily for at least 1 day, 2 days, 3 days, 15 days, 1 week, 2 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years or 10 years.

[0250] A subject's plasma endoxifen steady state level may be determined by measuring endoxifen in a test sample. The subject's plasma endoxifen steady state levels are compared to a reference plasma endoxifen level. For the purposes of the present disclosure, the reference plasma level is 30 nM. If the subject's plasma endoxifen level is determined to be lower than 30 nM, then the subject is defined as tamoxifen-refractory. Such a tamoxifen-refractory subject who has or who may be at risk of having a hormone-dependent breast disorder or hormone-dependent reproductive tract disorder is treated by administering to the subject an oral composition comprising (Z)-endoxifen or a salt thereof disclosed herein, or a polymorphic form of endoxifen disclosed herein. In some embodiments, the composition administered to such a subject comprises (Z)-endoxifen free base. In some embodiments, the composition administered to such a subject comprises a polymorphic form, such as Form I, Form II or Form III, of endoxifen. In other embodiments, the composition administered to such a subject comprises endoxifen gluconate selected from the group consisting of (Z)-endoxifen D-gluconate, (Z)-endoxifen L-gluconate, (E)-endoxifen D-gluconate, (E)-endoxifen L-gluconate, or a combination thereof. In other embodiments, the composition comprising endoxifen

is endoxifen HCl or endoxifen citrate. The present disclosure also contemplates that a subject's plasma endoxifen levels are tracked or monitored periodically or as necessary. If required, a subject who has been administered an initial dosage of tamoxifen may have his or her plasma endoxifen steady state levels adjusted by administering a composition comprising endoxifen on an ongoing basis based on the test results.

[0251] In some embodiments, the subject's tamoxifen-refractory status may be determined by determining the subject's tamoxifen-metabolites profile which is compared with a reference tamoxifen-metabolite profile as seen in control or normal subjects. Subjects with low plasma endoxifen levels in subject's tamoxifen-metabolite profile as compared to the reference tamoxifen-metabolite profile are administered an oral composition comprising endoxifen or a salt thereof. Such compositions may comprise synthetically prepared endoxifen.

[0252] The plasma endoxifen may be measured by any of method known in the art. The levels of plasma endoxifen in test sample may be determined based on subject's genes, DNA, RNA, protein, tamoxifen-metabolite profile or a combination thereof. The tamoxifen-metabolites profile can include at least tamoxifen, 4-OHT, N-desmethyltamoxifen, and/or endoxifen. In some embodiments, the level of plasma endoxifen and/or tamoxifen-metabolite profile in the test sample is measured by High Performance Liquid Chromatography (HPLC), Gas Chromatography Mass Spectrometry (GC-MS), Liquid Chromatography Mass spectrometry (LC-MS), Liquid Chromatography Tandem Mass spectrometry (LC-MS/MS), immunohistochemistry (IHC), polymerase chain reaction (PCR), quantitative PCR (qPCR), and the like. In some embodiments, the tamoxifen-metabolites profile is predicted based on the subject's genetic composition. In some embodiments, the subject's CYP genotype includes, without limitation, analysis of CYP2D6, CYP3A4, CYP2C9 genes. In some embodiments, subject's estrogen receptor levels may be analyzed. In other embodiments, the determination of plasma endoxifen may be done by a third party laboratory.

[0253] Accordingly, provided herein are methods of maintaining in a subject in need thereof a plasma endoxifen a level greater than 30 nM by administering to the subject a composition comprising endoxifen or a salt thereof. In some embodiments, the subject's plasma endoxifen level is maintained at a steady state level greater than 30 nM. In some embodiments, the subject's plasma endoxifen levels are maintained at a steady state level ranging from 30 nM to 300 nM (for example, from 30 nM to 200 nM, or from 30 nm to 80 nM). In some embodiments, the subject's plasma endoxifen levels are maintained at a steady state level >40 nM.

[0254] In another aspect, the subjects may have their test samples tested for their biomarker profile that may be indicative or monitoring a hormone-dependent breast disorder, a hormone-dependent

reproductive tract disorder, or both. Such biomarkers are known in the art and include, by way of non-limiting examples, biomarkers such as CYP2D6, BRCA-1, BRCA-2, ER, PR, Her2, uPA, PAI, Tf, p53, Ki67, cytokeratins, cancer tumor antigens, and other biomarkers measured by Mammaprint, OncotypeDx, PAM50, EndoxPredict, MammoStrat, and other diagnostic and predictive tests. A subject with biomarker profile indicating that the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both can be administered a composition disclosed herein. In one aspect, the present disclosure provides a method of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, comprising determining a subject's tamoxifen-refractory or tamoxifen-resistant status and administering to the subject a composition described herein.

[0255] In some aspects, provided herein are methods of treating a tamoxifen-refractory or tamoxifen-resistant subject, the method comprising administration to the subject a composition comprising endoxifen, or a salt or polymorph thereof.

[0256] In some embodiments disclosed herein are methods of treating a tamoxifen-refractory subject having or at risk for having a hormone-sensitive breast disorder, a hormone-sensitive reproductive tract disorder, or both, the method comprising administration to the subject an oral composition comprising endoxifen, or a salt thereof, wherein the subject has plasma endoxifen level of less than 30 nM, less than 25 nM, less than 20 nM, less than 15 nM, less than 10 nM, less than 5 nM or less than 1 nM. In certain embodiments, the composition comprising endoxifen salt is endoxifen gluconate, endoxifen HCl, or endoxifen citrate. In other embodiments, an oral solid dosage form comprising at least 90% (Z)-endoxifen or a salt thereof is administered. In other embodiments, an oral solid dosage form comprising at least 90% of polymorph Form I, Form II, or Form III of endoxifen is administered.

[0257] Also provided herein are methods of treating a tamoxifen-refractory subject, the method comprising: (a) determining or having determined plasma endoxifen level in a test sample obtained from the subject; (b) comparing or having compared or having determined the level of plasma endoxifen in the test sample with a reference plasma endoxifen level; (c) determining or having determined a reduced level of plasma endoxifen in the test sample as compared to the reference plasma endoxifen level; and (d) administering a composition comprising endoxifen or a salt or polymorph thereof to the subject. The administration of a composition comprising endoxifen or a salt or polymorph thereof maintains the levels of plasma endoxifen in the subject at steady state

levels greater than 30 nM. In some embodiments, the levels of plasma endoxifen in the subject are maintained at steady state levels ranging from 30 nM to 80 nM.

[0258] Provided herein are methods of treating a subject having or at risk of having a hormonal dependent breast disorder or a hormonal dependent reproductive tract disorder, the method comprising: (a) administering to the subject a first composition comprising tamoxifen; (b) determining or having determined the level of plasma endoxifen in a test sample obtained from the subject; (c) determining or having determined reduced level of plasma endoxifen in test sample as compared to a reference level of plasma endoxifen; and (d) administering an oral composition disclosed herein to the subject. The subject may be administered with the first composition comprising tamoxifen daily for at least 1 day, 2 days, 3 days, 15 days, 1 week, 2 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 1 year, 2 years, 3 years, 4 years, 5 years or 10 years. In some embodiments, administration of the oral composition comprising endoxifen or a salt or polymorph thereof maintains the subject's plasma endoxifen at levels greater than 30 nM. In other embodiments, administration of the oral composition comprising endoxifen or a salt or polymorph thereof maintains the subject's plasma endoxifen at levels ranging from 30 nM to 300 nM (e.g., from 30 nM to 200 nM, or from 30 nM to 80 nM). In some embodiments, the subject is administered an oral composition comprising (Z)-endoxifen D-gluconate, (Z)-endoxifen L-gluconate, (E)-endoxifen D-gluconate, (E)-endoxifen L-gluconate, or a combination thereof. In other embodiments, the oral composition comprising endoxifen salt is endoxifen HCl or endoxifen citrate. In some embodiments, the subject is administered an oral composition comprising polymorph Form I, Form II or Form III of endoxifen disclosed herein.

[0259] Provided herein are methods of treating a subject with a hormone-dependent breast disorder or hormone-dependent reproductive tract disorder, the method comprising: (a) dosing the subject with a first composition comprising tamoxifen; (b) determining or having determined the subject's tamoxifen-metabolites profile in a test sample obtained from the subject; (c) determining a reduced level of subject's plasma endoxifen based on the subject's tamoxifen-metabolites profile to compared to a level of reference plasma endoxifen in a reference tamoxifen-metabolites profile; and (d) administering an oral composition comprising endoxifen or a salt or polymorph thereof to the subject. In certain embodiments, the composition comprising endoxifen is endoxifen gluconate, endoxifen HCl, or endoxifen citrate. In some embodiments, the composition comprises polymorph Form I, Form II, or Form III of endoxifen.

[0260] Provided herein are methods for adjusting plasma endoxifen levels in a subject being treated for hormone-dependent breast disorder or hormone-dependent reproductive tract disorder who has

one or more CYP2D6 or CYP3A4 mutations or has previously administered with initial dosage of tamoxifen, and who has a plasma endoxifen level less than reference plasma endoxifen level, the method comprising: (a) measuring the subject's plasma endoxifen level after initial dosage of tamoxifen; (b) comparing the subject's plasma endoxifen levels to the reference plasma endoxifen level; (c) administering an oral composition comprising endoxifen or a salt or polymorph thereof to the subject to maintain the subject's plasma endoxifen level at levels greater than 30 nM. In some embodiments, administration of the oral composition comprising endoxifen or a salt or polymorph thereof maintains the subject's plasma endoxifen at levels ranging from 30 nM to 300 nM (e.g., from 30 nM to 200 nM, or from 30 nM to 80 nM). In some embodiments, the subject's plasma endoxifen level is maintained at a steady state level. The subject may be administered with initial dosage of tamoxifen daily for at least 1 day, 2 days, 3 days, 15 days, 1 week, 2 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months.

[0261] Provided herein are methods for adjusting the level of plasma endoxifen in a subject being treated for hormone-dependent breast disorder or hormone-dependent reproductive tract disorder who has been previously administered an initial dosage of tamoxifen and who has a level of plasma endoxifen less than 30 nM, the method comprising: (a) measuring the level of plasma tamoxifen-metabolite endoxifen of the subject after the initial dosage of tamoxifen; (b) comparing the plasma level of tamoxifen-metabolite endoxifen to the reference level for normal tamoxifen-metabolite endoxifen level; (c) administering an adjusting dosage of a composition comprising synthetically prepared endoxifen, wherein the dosage of synthetically prepared endoxifen is sufficient to maintain the subject's plasma endoxifen at a level greater than 30 nM. In some embodiments, administration of the second composition comprising a synthetically prepared endoxifen maintains the subject's plasma endoxifen at levels ranging from 30 nM to 300 nM (e.g., from 30 nM to 200 nM, from 30 nM to 80 nM). In some embodiments, the steps (a) to (c) may be repeated until the subject exhibits a desired plasma level of endoxifen.

[0262] In an aspect, the present disclosure contemplates a method of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, the method comprising resection of breast tissue of the subject or administering radiotherapy to the subject and administering an oral composition comprising endoxifen or a salt or polymorph thereof disclosed herein. In another aspect, the present disclosure contemplates a method of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, the method comprising administering an oral

composition disclosed herein prior to resection of breast tissue of the subject or administering radiotherapy to the subject.

[0263] Dosage to be administered to a subject will be usually in a unit dosage form. Examples of ranges for endoxifen in each dosage unit form are from 0.01 mg to 200 mg. Dosage shall generally be an effective amount and equivalent, on a molar basis, of the pharmacologically active (Z)-free form produced by a dosage formulation upon metabolic release of the active free drug to achieve its desired pharmacological and physiological effects. In some embodiments, the compositions comprising endoxifen or an endoxifen salt or polymorph are administered to the subject at a dose of 0.01 mg to 200.0 mg. In other embodiments, the oral compositions comprising endoxifen or an endoxifen salt or polymorph are administered to the subject at a dose of 1 mg to 200.0 mg. In some embodiments, the oral compositions comprising endoxifen or an endoxifen salt or polymorph are administered to the subject at a dose of 0.01 mg, 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg, 4.0 mg, 6 mg, 8 mg, 10 mg, 20 mg, 40 mg, 50 mg, 100 mg or 200 mg per unit dose. In certain embodiments, the oral compositions comprising at least 90% (Z)-endoxifen (wt/wt) of endoxifen are administered at a dose of 1 mg, 2.0 mg, 4.0 mg 6 mg, 8 mg, 10 mg, 20 mg, 40 mg, 50, 100 mg or 200 mg per unit dose. In some embodiments, the compositions comprising endoxifen gluconate are administered at a dose ranging from 0.01 to 20 mg. In some embodiments, a composition comprising (Z)-endoxifen D-gluconate is administered at 0.5 mg, 1 mg, 2 mg 4.0 mg, 6 mg, 8 mg, 10 mg, 20 mg, 40 mg, 50 mg, 100 mg, and 200 mg per unit dose. In some embodiments, a composition comprising 1 mg of (Z)-endoxifen D-gluconate is administered. In other embodiments, a composition comprising 1 mg of (Z)-endoxifen L-gluconate is administered. In yet other embodiments, a composition comprising 2 mg of (Z)-endoxifen D-gluconate and (E)-endoxifen D-gluconate is administered. In certain embodiments, an oral composition comprising at least 90% of a polymorph, such as polymorph Form I, Form II or Form III, of endoxifen (wt/wt) is administered at a dose of 1 mg, 2.0 mg, 4.0 mg 6 mg, 8 mg, 10 mg, 20 mg, 40 mg, 50, 100 mg or 200 mg per unit dose. In some embodiments, a composition comprising a polymorphic form, such as Form I, Form II or Form III, of endoxifen is administered at a dose ranging from 0.01 to 20 mg.

[0264] Breast cancer growth rate studies have shown, using mammographic screening of subjects with breast cancer, that the breast cancer growth rate in the 25th percentiles of women ages 50 to 59 indicate an unmet need for fast exposure of the subject to therapeutics (Weeden-Fekjaer et al. Breast Cancer Research200810:R41). Rapid absorption and bioavailability of the anti-cancer therapeutics such as endoxifen that can further reduce the cancer growth rate is highly desirable.

[0265] In one aspect, rapid achievement of maximal and steady state plasma levels of endoxifen is a particular aspect of the present disclosure. The present disclosure provides that administration of compositions disclosed herein to a subject achieves a maximal plasma level of endoxifen ranging within 2 to 30 hours, within 3 to 20 hours, within 2 to 10 hours or within 4 to 8 hours after administration of the compositions. Accordingly, in some embodiments, time to maximal (peak) plasma level of endoxifen ranges from 2 to 10 hours after administration of the compositions. In some embodiments, the time to maximal plasma level of endoxifen ranges from 4 to 8 hours after administration of composition disclosed herein.

[0266] Rapid achievement of steady-state plasma levels of endoxifen is also highly desirable. Plasma levels of endoxifen in a subject administered with a composition disclosed herein comprising (Z)-endoxifen or a salt or polymorph thereof rapidly achieves steady state. Steady state plasma levels can be achieved from day 7 to day 21. In some embodiments, the steady state plasma levels can be achieved by day 7 (Figure 5) following daily administration of a composition disclosed herein.

[0267] In an aspect, the present provides that circulating endoxifen released from compositions disclosed herein can be cleared faster than tamoxifen. Terminal elimination half life of tamoxifen is said to be 5-7 days (Jordan C. Steroids. 2007 Nov; 72(13): 829–842) and peak concentration time of tamoxifen is approximately 5 hours post-dose. Endoxifen released from a composition disclosed herein can have a terminal elimination half-life ranging from 30 to 60 hours, significantly lower than tamoxifen. In some embodiments, the mean half -life ranges from 40 to 53 hours. Mean Ratio of AUC_{24hr} (Day 21)/$AUC_{0\text{-}inf}$ (Day1) typically ranges from 0.7 to 1.2 for compositions comprising 1 mg to 4 mg (Z)-endoxifen or a salt or polymorph thereof. Thus, accumulation of endoxifen released from the compositions disclosed herein do not significantly vary over continued treatment.

[0268] In another aspect, the present disclosure provides that administration of compositions disclosed herein achieve absorption of endoxifen that is therapeutically effective.

[0269] Area under Curve $AUC_{(0\text{-}24hr)}$ ("AUC_{24hr}") describes the total exposure of the subject to a drug from time of dosing (0 hr) over a 24 hour period. Compositions comprising (Z)-endoxifen or a salt thereof typically achieve mean (AUC_{24hr}) of 150 hr*ng/mL to 600 hr*ng/mL on Day 1 of initial (first) dose of compositions comprising 1 mg to 4 mg of (Z)-endoxifen. Compositions comprising (Z)-endoxifen or salts thereof typically achieve mean AUC_{24hr} of 400 hr*ng/mL to 2500 hr*ng/mL on Day 21 of initial (first) dose of compositions comprising 1 mg to 4 mg of (Z)-endoxifen.

[0270] $AUC_{(0\text{-}inf)}$ ("$AUC_{0\text{-}inf}$"), a time-averaged concentration of drug circulating in the body fluid analyzed (normally plasma, blood or serum), describes the total exposure of the subject to a drug.

The present provides that the exposure of subjects to endoxifen ($AUC_{0\text{-}inf}$) can be dose proportional. In some embodiments, $AUC_{0\text{-}inf}$ ranges from 200 hr*ng/mL to 10000 hr*ng/mL. In other embodiments, the $AUC_{0\text{-}inf}$ ranges from 300 hr*ng/mL to 8000 hr*ng/mL. In certain embodiments, the $AUC_{0\text{-}inf}$ ranges from 400 hr*ng/mL to 6000 hr*ng/mL over the dosing range of 1 mg to 4 mg of (Z)-endoxifen (for example, see **Table 17**).

[0271] A healthcare professional, such as an attending physician, may adjust the dosing regimen based on the pharmacokinetic profile of the composition in the subject.

[0272] In one aspect, the compositions of the disclosure can be used alone or in a combination therapy. For example, compositions disclosed herein may be used in combination with one or more therapeutic agents as part of primary therapy, neoadjuvant therapy, or an adjuvant therapy. It is an aspect of the present disclosure that the compositions of the disclosure can be used in combination with other therapies such as surgery and radiation as neo-adjuvant or adjuvant therapy. Combinations of the compositions may act to improve the efficacy of the therapeutic agents, and therefore can be used to improve standard cancer therapies. For example, when a subject has prostate cancer and is on bicalutamide or enzalutamide therapy for the treatment of prostate cancer, the subject is likely to develop gynecomastia a result of the therapy. The compositions disclosed herein can be administered as a combination therapy to the subject having prostate cancer in order to prevent and/or treat gynecomastia. As another example, a subject with ER+/Her2+ positive breast cancer would be on a combination therapy with trastuzumab or other oncology drugs such as anti-neoplastics or immunotherapy, and a composition disclosed herein can be used to treat such a subject with ER+/Her2+ positive breast cancer. Accordingly, in some embodiments, the compositions further comprise bicalutamide, enzalutamide or anticancer drugs such as trastuzumab, antineoplastics such as capecitabine (Xeloda), carboplatin (Paraplatin), cisplatin (Platinol), cyclophosphamide (Neosar), docetaxel (Docefrez, Taxotere), doxorubicin (Adriamycin), pegylated liposomal doxorubicin (Doxil), epirubicin (Ellence), fluorouracil (5-FU, Adrucil), gemcitabine (Gemzar), methotrexate (multiple brand names), paclitaxel (Taxol), protein-bound paclitaxel (Abraxane), vinorelbine (Navelbine), eribulin (Halaven), ixabepilone (Ixempra), and ATP-cassette binding protein inhibitors.

[0273] In another aspect, a composition disclosed herein may comprise therapeutic agents that increase bioavailability of endoxifen in a subject. P-glycoprotein (P-gp, ABCB1) is a highly efficient drug efflux pump expressed in brain, liver, and small intestine, but also in cancer cells, that affects pharmacokinetics and confers therapy resistance for many anticancer drugs. Accordingly, in some embodiments, the compositions further comprise inhibitors of ATP-binding cassette (ABC

family) transporters, such as inhibitors of breast cancer resistance protein (BCRP protein) and P-gp. Several inhibitors of BCRP protein and P-Gp are known in the art. For example, inhibitors of BCRP protein include cyclosporine, omeprazole, pantoprazole, saquinavir, and tacrolimus.

[0274] Non-limiting examples of P-gp inhibitors include first generation inhibitors such as Verapamil, cyclosporin A, reserpine, quinidine, yohimbine, tamoxifen and toremifene, second generation inhibitors such as Dexverapamil, dexniguldipine, valspodar (PSC 833), and Dofequidar fumarate (MS-209), third generation P-gp inhibitors such as Cyclopropyldibenzosuberane zosuquidar (LY335979), laniquidar (R101933), mitotane (NSC-38721), biricodar (VX-710), elacridar (GF120918/GG918), ONT-093, tariquidar (XR9576), and HM30181 and anti-P-gp monoclonal antibodies such as MRK-16).

[0275] The present disclosure additionally provides for therapeutic kits containing one or more of the compositions for use in the treatment of a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both. The kits of the present disclosure may include an oral composition disclosed herein, a sealed container for housing the composition, and instructions for use of the orally administered composition. In an aspect, the kits of the present disclosure can include a second therapeutic agent. Such a second therapeutic agent may be bicalutamide, enzalutamide or an anticancer drug such as trastuzumab, antineoplasitcs such as capecitabine (Xeloda), carboplatin (Paraplatin), cisplatin (Platinol), cyclophosphamide (Neosar), docetaxel (Docefrez, Taxotere), doxorubicin (Adriamycin), pegylated liposomal doxorubicin (Doxil), epirubicin (Ellence), fluorouracil (5-FU, Adrucil), gemcitabine (Gemzar), methotrexate (multiple brand names), paclitaxel (Taxol), protein-bound paclitaxel (Abraxane), vinorelbine (Navelbine), eribulin (Halaven), ixabepilone (Ixempra), and ATP-binding cassette (ABC transporter) inhibitors such as P-gp inhibitors.

Exemplary Compositions

[0276] Exemplary, non-limiting compositions are provided below. As mentioned above, percentages (%) refer to amounts by weight based upon the total weight of the composition (wt/wt). The sum of the different components of the composition adds up to 100% (wt/wt) of the total composition. The at least 90% (≥90%) (Z)-endoxifen free base refers to the percent weight of (Z)-endoxifen isomer as compared to the total weight of endoxifen in any composition.

[0277] In an aspect, the present disclosure relates to industrially scalable processes for manufacturing (Z)-endoxifen, compounds of Formula (III), the compound of Formula (II), and salts and polymorphs thereof.

[0278] In an aspect, the present disclosure relates to an industrially scalable process for manufacturing (Z)-endoxifen, comprising the steps of: (a) reacting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), to 6N HCL (1:1 to 1:5 wt/wt) in EtOAc (1:1 to 1:20 wt/wt), (b) neutralizing with 8N NaOH (1:1 to 1:20 wt/wt); (c) washing one or more times with EtOAc (1:1 to 1:10 wt/wt); (d) extracting with 20% NaCl (1:1 to 1:5 wt/wt); (e) reacting with activated carbon (1:0.01 to 1:1); (f) washing one or more times with IPA (1:1 to 1:10 wt/wt) and extracting with MeOH/PPW (1:1 to 1:10 wt/wt); wherein the wt/wt is with respect to the mixture of (E)-endoxifen and (Z)-endoxifen, e.g., compounds of Formula (III).

[0279] In an aspect, the present disclosure relates to an industrially scalable process for manufacturing a mixture of (E)-endoxifen and (Z)-endoxifen (compounds of Formula (III)), comprising: (a) reacting the compound of Formula (II) with propiophenone in THF (4.4 wt/wt); (b) preparing a solution of $TiCl_4$ (1.4 wt/wt) and Zn (0.9 wt/wt) in THF (8.9 wt/wt); and (c) reacting the compound of Formula (II) of step (a) with $TiCl_4$ and Zn in THF from step (b) to form a mixture of (E)-endoxifen and (Z)-endoxifen; wherein wt/wt is with respect to the compound of Formula (II).

[0280] In an aspect, the present disclosure relates to an industrially scalable process for manufacturing a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), comprising one or more steps of : (a) extraction with 25% ammonium chloride (1:20 wt/wt) and silica (Celite) (1:1 wt/wt); (b) one or more washes with THF (1:1 to 1:5 wt/wt); (c) one or more washes with 20% sodium chloride (1:3 wt/wt); (c) distillation with EtOAc (1:4.5 wt/wt); and (d) crystallization with (1:2 v/v) EtOAc/n-heptane (1:3.8 wt/wt); wherein the wt/wt is with respect to the compound of Formula (II).

[0281] In an aspect, the present disclosure relates to an industrially scalable process for manufacturing a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), further comprising one or more steps of: (a) extraction one or more times with 40% K_2CO_3 (1:2 wt/wt); (b) extraction with 1N NaOH (1:10 wt/wt) and MeTHF (1:1 to 1:10 wt/wt); (c) two more extractions with MeTHF (1:1 to 1:20 wt/wt); (d) extraction with 20% sodium chloride (1:5 wt/wt); (e) distillation with IPA (1:4.5 wt/wt); and (f) crystallization with (1:2.7 v/v) IPA/n-heptane (1:3.4 wt/wt); wherein the wt/wt is with respect to the compound of Formula (II).

[0282] In an aspect, the present disclosure relates to an industrially scalable process for manufacturing the compound of Formula (II), comprising the steps of: (a) reacting the compound of Formula (I) (1 equiv.) with DIPEA (3 wt/wt) in THF (4.9 wt/wt); (b) adding 1-chloroethyl chloroformate (3.3 wt/wt); (c) distilling one to five times with methanol (4.0 wt/wt); (d) distilling with methanol (3.2 wt/wt); (e) reacting with methanol (3.2 wt/wt)/6N HCl (4 wt/wt); and (f)

neutralizing with 8N NaOH (5 wt/wt); and wherein wt/wt is with respect to the compound of Formula (I).

[0283] In an aspect, the present disclosure relates to (Z)-endoxifen, (E)-endoxifen, compounds of Formula (III), and the compound of Formula (II), and salts thereof, prepared according to processes described herein. In an aspect, the present disclosure relates to (Z)-endoxifen prepared according to a process disclosed herein, wherein the (Z)-endoxifen is stable at ambient temperature for at least 6 months, at least 9 months, at least 12 months, or at least 18 months.

[0284] In another aspect, the (Z)-endoxifen free based prepared in accordance with the processes disclosed herein have <1% impurity. In still another aspect, the (E)/(Z)-endoxifen free base prepared in accordance with the processes disclosed herein has <1% impurity.

[0285] In an aspect, the present disclosure relates to compositions comprising (Z)-endoxifen free base or a salt thereof prepared according to any of the methods disclosed herein.

[0286] In another aspect, the present disclosure relates to compositions comprising (Z)-endoxifen free base or a salt thereof prepared according to any of the methods disclosed herein, wherein the (Z)-endoxifen is at least 90% (Z)-endoxifen free base wt/wt of total endoxifen in the composition.

[0287] In still another aspect, the compositions further comprise (E)-endoxifen, wherein the ratio of (E)-endoxifen to (Z)-endoxifen (E/Z-ratio) is 1:99; 5:95; 10:90, 15:85; 20:80, 25:75; 30:70; 40:70, 45:55; 50:50; 55:45; 60:40; 65:45; or 70:30.

[0288] In a further aspect, the compositions further comprise (E)-endoxifen, wherein the E/Z-ratio ranges from 45:55 to 55:45 or is approximately 1:1.

[0289] In an aspect, the compositions comprise (Z)-endoxifen or a salt or polymorph thereof prepared according to any of the methods disclosed herein, wherein the (Z)-endoxifen is stable at ambient temperature for at least 6 months, at least 9 months, at least 12 months or at least 18 months;

[0290] In another aspect, the compositions comprise (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein,

a. wherein the compositions have aerobic bacterial plate count of not more than 20,000 g/mL;
b. wherein water content of the compositions is not more than 1.0% as tested by Method Ic of the USP 921;
c. wherein the water activity (Aw) of the compositions is less than 0.9,
d. wherein the residue on ignition is not more than 0.1% as tested by a method of USP 281;

e. wherein a heavy metal is not more than 20 ppm as tested by Method II of USP 231; or

f. wherein methanol is NMT 3000 ppm, tetrahydrofuran is NMT 720 ppm, isopropanol is NMT 5000 ppm, ethyl acetate is NMT 5000 ppm; n-Heptane is NMT 5000 ppm, and ethanol is NMT 5000 ppm as tested by a validated HPLC method

[0291] In still another aspect, the compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein comprise 0.01 mg to 200 mg (Z)-endoxifen or a salt or polymorph thereof per unit dose.

[0292] In yet another aspect, the compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein comprise 1 mg to 20 mg of (Z)-endoxifen or a salt or polymorph thereof per unit dose.

[0293] In a further aspect, the compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein comprise 0.01% to 20% (wt/wt) of endoxifen or a salt or polymorph thereof.

[0294] In a still further aspect, the present disclosure relates to compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition comprises 0.1% to 10% (wt/wt) of (Z)-endoxifen or a salt or polymorph thereof.

[0295] In another aspect, the present disclosure relates to compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein further comprising one or more excipient.

[0296] In yet another aspect, the present disclosure relates to compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, further comprising one or more excipient, wherein the excipient is a binder, a filler, a disintegrating agent, a lubricant, a glidant, a control release agent, an enteric coating agent, a film forming agent, a plasticizer, a sweetening agent, a flavoring agent, or a combination thereof.

[0297] In still another aspect, the present disclosure relates to compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, further comprising one or more excipient, wherein the excipients are about 0.1% to about 99% wt/wt of the composition.

[0298] In a further aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition comprises one or more control release agents selected from the group consisting of acid-insoluble polymers, methyl acrylate-methacrylic acid copolymers, cellulose acetate phthalate (CAP), cellulose

acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate (hypromellose acetate succinate), polyvinyl acetate phthalate (PVAP), methyl methacrylate-methacrylic acid copolymers, shellac, cellulose acetate trimellitate, sodium alginate, zein, waxes, including synthetic waxes, microcrystalline waxes, paraffin wax, carnauba wax, and beeswax, polyethoxylated castor oil derivatives, hydrogenated oils, glyceryl mono-, di- tribenates, glyceryl monostearate, glyceryl distearate, long chain alcohols, such as stearyl alcohol, cetyl alcohol, polyethylene glycol, and mixtures thereof.

[0299] In one aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral, parenteral, topical, and intraductal delivery.

[0300] In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition formulated for oral delivery is a tablet, a caplet, a capsule, a pill, a powder, a troche, an elixir, a suspension, a syrup, a wafer, a chewing gum, a dragee, and a lozenge.

[0301] In yet another aspect, the present disclosure relates to compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the compositions formulated for oral delivery are tablets formulated as enteric tablets, caplets formulated as enteric caplets, and capsule formulated as enteric capsules.

[0302] In yet another aspect, the present disclosure relates to compositions comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the compositions formulated for oral delivery are tablets formulated as delayed-release tablets, caplets formulated as delayed-release caplets, or capsules formulated as delayed-release capsules.

[0303] In yet another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or 701, the composition releases in stomach:

a. less than 10% of endoxifen in 2 hours after administration;
b. less than 20% of endoxifen in 2 hours after administration;
c. less than 30% of endoxifen in 2 hours after administration;
d. less than 40% of endoxifen in 4 hours after administration; or
e. less than 50% of endoxifen in 6 hours after administration.

[0304] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the

composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or 701, the composition releases in stomach:

a. less than 10% of (Z) endoxifen in 2 hours after administration;
b. less than 20% of (Z) endoxifen in 2 hours after administration;
c. less than 40% of (Z) endoxifen in 4 hours after administration; or
d. less than 50% of (Z) endoxifen in 6 hours after administration.

[0305] In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or 701, the composition releases at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% endoxifen in the intestines.

[0306] In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or 701, the composition releases in the intestines at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% endoxifen in 2 hours after administration.

[0307] In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or 701, the composition releases in the intestines at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% endoxifen in 3 hours after administration.

[0308] In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or 701, the composition releases in the intestines at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% endoxifen in 4 hours after administration.

[0309] In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711 or 701, the composition releases in small intestine:

a. at least 10% of endoxifen after 4 hours after administration;
b. at least 30% of endoxifen after 6 hours after administration;
c. at least 40% of endoxifen after 7 hours after administration;

d. at least 50% of endoxifen after 8 hours after administration;

e. at least 50% of endoxifen after 2 hours after administration;

f. at least 60% of endoxifen after 2 hours after administration;

g. at least 70% of endoxifen after 2 hours after administration;

h. at least 80% of endoxifen after 2 hours after administration; or

i. at least 90% of endoxifen after 2 hours after administration.

[0310] In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or salts thereof prepared according to any of the methods disclosed herein, wherein the composition is formulated for oral delivery, and wherein as tested by a method of USP 711, the composition is formulated to release at least 50% of endoxifen after 8 hours after administration in the colon.

[0311] In another aspect, the present disclosure relates to a composition formulated for oral administration comprising: 1 mg to 200 mg of endoxifen per unit dose; and wherein the composition is stable for at least 6 months.

[0312] In another aspect, the present disclosure relates to a composition formulated for oral administration comprising: 1 mg to 200 mg of endoxifen per unit dose;

wherein the endoxifen is at least 90% (Z)-endoxifen free base; and

wherein:

the composition has an aerobic bacterial plate count of not more than 20,000 g/ml;

water content of the (Z)-endoxifen is not more than 1% as determined by Method Ic of the USP 921;

residue on ignition of the (Z)-endoxifen is not more than 0.10% as tested by a method of USP 281; or

a heavy metal is not more than 20 ppm as tested by Method II of USP 231.

[0313] In another aspect, the present disclosure relates to a composition formulated for oral administration comprising: 1 mg to 200 mg of endoxifen per unit dose,

wherein the composition is formulated as an enteric tablet, an enteric caplet, and an enteric capsule;

wherein as determined by a method of USP 711, the composition is formulated to release in small intestine:

at least 25% of endoxifen after 4 hours after administration;

at least 30% of endoxifen after 6 hours after administration;

at least 40% of endoxifen after 7 hours after administration; or

at least 50% of endoxifen after 8 hours after administration; or

wherein as determined by a method of USP 711, the composition is formulated to release at least 50% of endoxifen in the colon.

[0314] In another aspect, the present disclosure relates to an oral solid dosage form composition comprising: 1 mg to 200 mg of endoxifen per unit dose;

wherein the endoxifen is at least 90% (Z)-endoxifen free base; and

wherein

the composition has an aerobic bacterial plate count of not more than 20,000 g/ml;

water content of the (Z)-endoxifen is not more than 1% as determined by Method Ic of the USP 921;

residue on ignition of the (Z)-endoxifen is not more than 0.10% as tested by a method of USP 281; or

a heavy metal is not more than 20 ppm as tested by Method II of USP 231; and

wherein the composition is formulated as an enteric tablet, an enteric caplet and an enteric capsule; and

wherein the endoxifen is neat; or

wherein the composition further comprises an excipient selected from the group consisting of a binder, a filler, a disintegrating agent, a lubricant, a glidant, a control release agent, an enteric coating agent, a film forming agent, a plasticizer, a colorant, a sweetening agent, and a flavoring agent, or a combination thereof.

[0315] In another aspect, the present disclosure relates to an enteric capsule, comprising (Z)-endoxifen free base prepared by a process described herein.

[0316] In another aspect, the present disclosure relates to an enteric capsule comprising 1 mg to 200 mg of neat endoxifen per unit dose:

wherein the endoxifen is at least 90% (Z)-endoxifen free base; and

wherein

the composition has an aerobic bacterial plate count of not more than 20,000 g/ml;

water content of the (Z)-endoxifen is not more than 1% as determined by Method Ic of the USP 921;

residue on ignition of the (Z)-endoxifen is not more than 0.10% as tested by a method of USP 281; and

a heavy metal is not more than 20 ppm as tested by Method II of USP 231.

[0317] In another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the

endoxifen salt is selected from the group consisting of arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, Teoclate, triethiodide, benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc.

[0318] In yet another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the endoxifen salt is endoxifen gluconate.

[0319] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the endoxifen salt is endoxifen gluconate selected from the group consisting of (Z)-endoxifen D-gluconate, (E)-endoxifen D-gluconate, (Z)-endoxifen L-gluconate, and (E)-endoxifen L-gluconate, or a combination thereof.

[0320] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the endoxifen salt is endoxifen gluconate, and wherein the endoxifen gluconate comprises 1%, 5%, 10%, 20%, 25%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.99% or 100% (wt/wt) of (Z)-endoxifen D-gluconate or (Z)-endoxifen L-gluconate.

[0321] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the endoxifen salt is endoxifen gluconate, and wherein the endoxifen gluconate comprises (Z)-endoxifen D-gluconate and (E)-endoxifen D-gluconate (wt/wt) at Z/E-ratio of 10:90, 20:80, 30:70; 40:60; 50:50, 60:40, 70:30, 80:20, 90:10; 91:9; 92:8; 93:7; 94:8; 95:5, 96:4, 97:3, 98:2, 99:1; 99.5:0.5; or 99.99:0.01.

[0322] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

[0323] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein for the

treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

[0324] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, wherein the hormone-dependent breast disorder is breast cancer.

[0325] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, wherein the hormone-dependent breast disorder is breast cancer and wherein the breast cancer is a pre-cancer, an early stage cancer, a non-metastatic cancer, a pre-metastatic cancer, a locally advanced cancer, or a metastatic cancer.

[0326] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is tamoxifen-refractory or tamoxifen resistant.

[0327] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject in need thereof.

[0328] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject in need thereof and wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

[0329] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject in need thereof, wherein the subject's hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast

disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

[0330] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject in need thereof, wherein the subject has breast cancer and wherein breast cancer is a pre-cancer, an early stage cancer, a non-metastatic cancer, a pre-metastatic cancer, a locally advanced cancer, or a metastatic cancer.

[0331] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject in need thereof, wherein the subject has prostate cancer and wherein the subject has or is about to initiate prostate cancer therapy.

[0332] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject in need thereof, wherein the subject has prostate cancer, and wherein the subject has or is at risk of having gynecomastia.

[0333] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject that has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, and wherein the subject's hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is tamoxifen-refractory or tamoxifen resistant.

[0334] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to the subject at a unit dose of 0.01 mg, 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg, 4 mg, 5 mg, 10 mg, 20 mg, 25 mg, 50 mg or 200 mg of (Z)-endoxifen.

[0335] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to the subject at a dose of 0.01 mg, 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg, 4 mg, 5 mg, 10 mg, 20 mg, 25 mg, 50 mg or 200 mg of (Z)-endoxifen.

[0336] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to the subject once a day, twice a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually.

[0337] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein administration of the composition orally maintains the subject's plasma endoxifen at a level greater than 30 nM.

[0338] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject as combination therapy.

[0339] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered as a primary therapy, a neo-adjuvant therapy, or an adjuvant therapy.

[0340] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject either alone in combination with a second therapeutic agent.

[0341] In still another aspect, the present disclosure relates to a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared by any of the processes described herein, wherein the composition is administered to a subject either alone in combination with a second therapeutic agent, and wherein the second therapeutic agent is bicalutamide, enzalutamide, or an anticancer drug such as trastuzumab, antineoplastic such as capecitabine (Xeloda), carboplatin (Paraplatin), cisplatin (Platinol), cyclophosphamide (Neosar), docetaxel (Docefrez, Taxotere), doxorubicin (Adriamycin), PEGylated liposomal doxorubicin (Doxil), epirubicin (Ellence), fluorouracil (5-FU, Adrucil), gemcitabine (Gemzar), methotrexate (multiple brand names), paclitaxel (Taxol), protein-bound paclitaxel (Abraxane), vinorelbine (Navelbine), eribulin (Halaven), ixabepilone (Ixempra), or inhibitors of ATP-binding cassette transporters.

[0342] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition prepared according to any one of the processes disclosed herein.

[0343] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein.

[0344] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

[0345] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

[0346] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the subject has breast cancer.

[0347] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the subject has breast cancer, and wherein the breast cancer is a pre-cancer, an early stage cancer, a non-metastatic cancer, a pre-metastatic cancer, a locally advanced cancer, or a metastatic cancer.

[0348] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

[0349] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the subject has

tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

[0350] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the composition is administered to the subject at a unit dose of 0.01 mg, 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg, 4 mg, 5 mg, 6 mg, 8 mg, 10 mg, 20 mg, 25 mg, 50 mg, 100 mg or 200 mg.

[0351] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the composition is administered once a day, twice, a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually.

[0352] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein administration of the composition orally maintains the subject's plasma endoxifen at a steady state level greater than 30 nM.

[0353] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein administration of the composition orally achieves the subject's plasma endoxifen at a steady state level greater than 30 nM by day 14 after the administration of the first dose (on day 1).

[0354] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof, wherein administration of the composition orally achieves the subject's plasma endoxifen at a steady state level greater than 30 nM by day 14 after the administration of the first dose (on day 1).

[0355] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein administration of the composition orally achieves a time to maximal plasma levels of endoxifen in the subject from 2 to 10 hours after administration (post-dose).

[0356] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph

thereof, wherein administration of the composition orally achieves a time to maximal plasma levels of endoxifen in the subject from 2 to 10 hours after administration (post-dose).

[0357] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof, wherein the mean terminal elimination half-life of endoxifen in the subject ranges from 30 to 60 hours post dose.

[0358] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof, wherein the mean terminal elimination half-life of endoxifen in the subject ranges from 40 to 55 hours post dose.

[0359] In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, the method comprising administering an oral composition comprising (Z)-endoxifen or a salt or polymorph thereof, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;
b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and
c. a steady state plasma level of endoxifen greater than 30 nM.

[0360] In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer, the method comprising administering an oral composition comprising (Z)-endoxifen or a salt or polymorph thereof, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;
b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and
c. a steady state plasma level of endoxifen greater than 30 nM.

[0361] In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancera and vulvar cancer, the method comprising administering an oral composition comprising (Z)-endoxifen or a salt or polymorph thereof formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet, or a delayed-release capsule, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;
b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and
c. a steady state plasma level of endoxifen greater than 30 nM.

[0362] In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer, the method comprising administering an oral composition comprising (Z)-endoxifen or a salt or polymorph thereof formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet, or a delayed-release capsule, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;
b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and
c. a steady state plasma level of endoxifen greater than 30 nM; and

wherein at least 50%, at least 60%, at least 70%, at least 80% or at least 90% of the endoxifen is released in the intestines.

[0363] In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer, the method comprising administering an oral composition comprising 0.01 mg to 200 mg of (Z)-endoxifen or a salt or polymorph thereof formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet, or a delayed-release capsule, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;
b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and
c. a steady state plasma level of endoxifen greater than 30 nM; and

wherein at least 50%, at least 60%, at least 70%, at least 80% or at least 90% of the endoxifen is released in the intestines.

[0364] In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer, the method comprising administering daily an oral composition comprising 0.01 mg to 200 mg of (Z)-endoxifen or a salt or polymorph thereof formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet, or a delayed-release capsule, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;
b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and
c. a steady state plasma level of endoxifen greater than 30 nM.

[0365] In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer, the method comprising administering daily an oral composition comprising 0.01 mg to 200 mg of (Z)-endoxifen or a salt or polymorph thereof formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet, or a delayed-release capsule, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;
b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and
c. a steady state plasma level of endoxifen greater than 30 nM; and

wherein at least 50%, at least 60%, at least 70%, at least 80% or at least 90% of the endoxifen is released in the intestines.

[0366] In another aspect, the present disclosure relates to a method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer, the method comprising administering daily an oral composition comprising 0.01 mg to 200 mg of (Z)-endoxifen or a salt or polymorph thereof formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet, or a delayed-release capsule, wherein administration of the composition achieves:

a. a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;
b. a time to maximum plasma levels of endoxifen ranging from 2 hours to 10 hours after administration; and
c. a steady state plasma level of endoxifen greater than 30 nM;

wherein the mean area under the curve extrapolated to time infinity (AUC_{0-inf}) is 200 hr*ng/mL to 10000 hr*ng/mL, 300 hr*ng/mL to 8000 hr*ng/mL, 400 hr*ng/mL to 6000 hr*ng/mL or 700 hr*ng/mL to 6000 hr*ng/mL; and

wherein at least 50%, at least 60%, at least 70%, at least 80% or at least 90% of the endoxifen is released in the intestines.

[0367] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein the method is a primary therapy, a neo-adjuvant therapy, or an adjuvant therapy.

[0368] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein a composition is administered to a subject as combination therapy.

[0369] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein a composition is administered to a subject either alone in combination with a second therapeutic agent.

[0370] In still another aspect, the present disclosure relates to a method of treating a subject in need thereof comprising administering a composition comprising (Z)-endoxifen or a salt or polymorph thereof prepared according to any one of the processes disclosed herein, wherein a composition is administered to a subject with a second therapeutic agent selected from the group consisting of bicalutamide, enzalutamide, or an anticancer drug such as trastuzumab, antineoplastics such as capecitabine (Xeloda), carboplatin (Paraplatin), cisplatin (Platinol), cyclophosphamide (Neosar), docetaxel (Docefrez, Taxotere), doxorubicin (Adriamycin), PEGylated liposomal doxorubicin (Doxil), epirubicin (Ellence), fluorouracil (5-FU, Adrucil), gemcitabine (Gemzar), methotrexate (multiple brand names), paclitaxel (Taxol), protein-bound paclitaxel (Abraxane), vinorelbine (Navelbine), eribulin (Halaven), ixabepilone (Ixempra), and ATP-cassette binding protein transport inhibitors.

[0371] In still another aspect, the present disclosure relates to a use for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, in a subject, the use comprising:

dosing the subject with a first composition comprising tamoxifen;

determining the subject's tamoxifen-metabolites profile in a test sample obtained from the subject;

determining a reduced level of subject's plasma endoxifen based on subject's tamoxifen-metabolites profile as to compared to a level of plasma endoxifen in a reference tamoxifen-metabolites profile; and

administering to the subject a composition of the present disclosure.

[0372] In still another aspect, the present disclosure relates to a use for the treatment and prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, in a subject, the use comprising:

dosing the subject with a first composition comprising tamoxifen;

determining the subject's tamoxifen-metabolites profile in a test sample obtained from the subject;

determining a reduced level of subject's plasma endoxifen based on subject's tamoxifen-metabolites profile as to compared to a level of plasma endoxifen in a reference tamoxifen-metabolites profile; and

administering to the subject a composition of the present disclosure;

wherein the composition is administered orally in a dose sufficient to maintain the subject's plasma endoxifen at a steady state level greater than 30 nM;

wherein the tamoxifen-metabolites profile comprises a panel of at least tamoxifen, 4-hydroxytamoxifen, n-desmethyltamoxifen, or endoxifen;

wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer;

wherein the hormone-dependent breast disorder is a pre-cancer, an early stage cancer, a non-metastatic cancer, a pre-metastatic cancer, a locally advanced cancer, or metastatic cancer;

wherein the hormone-dependent breast disorder is a non-metastatic cancer;

wherein the subject has prostate cancer, and wherein the subject further has or is at risk of having gynecomastia; or

wherein the hormone-dependent breast disorder or hormone-dependent reproductive tract disorder is tamoxifen-refractory or tamoxifen resistant.

[0373] In still another aspect, the present disclosure relates to a kit for treating a subject having or at risk of having a hormone-dependent breast disorder or hormone dependent reproductive tract disorder, in a subject in need thereof comprising: (a) a composition of the present disclosure; and (b) a sealed container for housing the composition; and c) instructions for use of the orally administered composition.

[0374] In still another aspect, the present disclosure relates to a kit for treating a subject having or at risk of having a hormone-dependent breast disorder or hormone dependent reproductive tract disorder, in a subject in need thereof comprising: (a) a composition of the present disclosure; and (b) a sealed container for housing the composition; and c) instructions for use of the orally administered composition, wherein the kit comprises a second therapeutic agent selected from the group consisting of bicalutamide, enzalutamide and anticancer drugs such as trastuzumab, antineoplastics such as capecitabine (Xeloda), carboplatin (Paraplatin), cisplatin (Platinol), cyclophosphamide (Neosar), docetaxel (Docefrez, Taxotere), doxorubicin (Adriamycin), PEGylated liposomal doxorubicin (Doxil), epirubicin (Ellence), fluorouracil (5-FU, Adrucil), gemcitabine (Gemzar), methotrexate (multiple brand names), paclitaxel (Taxol), protein-bound paclitaxel (Abraxane), vinorelbine (Navelbine), eribulin (Halaven), ixabepilone (Ixempra), and ATP-cassette binding protein transport inhibitors.

[0375] In still another aspect, the present disclosure relates to a method of administering a composition prepared in accordance with any of the processes described herein to a subject in need thereof in accordance with instructions for use comprised in a kit comprising the composition.

EXAMPLES

[0376] Abbreviations used herein

ACN/PPW = Acetonitrile/Process Purified Water

$NaHCO_3$ = Sodium hydrocarbonate

HCl = hydrochloric acid

THF = Tetrahydrofuran

MeTHF = 2-Methyltetrahydrofuran

CH_2Cl_2 = Dicholoromethane

EtOH = Ethanol

MeOH = Methanol

EtOAc = Ethyl acetate

IPA = Isopropyl alcohol; isopropanol

TFA = Trifluoroacetic acid

TCA = Trichloroacetic acid

PPW = Process Purified Water

IPA/PPW = Isopropyl alcohol/Process Purified Water

Example 1: ***Enrichment and Preparation of (Z)-Endoxifen Free Base***

A. Fractional Crystallization

[0377] (Z)-Endoxifen free base (drug substance) can be prepared from a mixture of (E)-endoxifen and (Z)-endoxifen by fractional crystallization described herein. Briefly, commercially available crude endoxifen mixture of (E)-endoxifen and (Z)-endoxifen isoforms (Astatech Ltd. China) were used as starting material to prepare (Z)-endoxifen as free base.

[0378] i. An E/Z-endoxifen solution was prepared by suspending 1 g of endoxifen having (E)-endoxifen and (Z)-endoxifen at ratios (E/Z ratio) of 51/1, 1/1.8, and 1/5.8, each in a 10x volume of the solvent, isopropanol (IPA). A second set of solutions was prepared by suspending 1 g each of endoxifen at E/Z ratios of 51/1, 1/1.8, and 1/5.8 in 10x volume of the solvent EtOAc. The solutions were heated to a first temperature of 50 °C creating a hot slurry and stirred overnight at 50 °C. The hot slurry samples were filtered using a cellulose filter pore size 0.5 µm. The mixtures were then cooled to a second temperature, room temperature 23 °C while stirring for 12 hours to effect crystallization. The aliquots of cooled samples were filtered using a cellulose filter pore size 0.5 µm. Aliquots of the solid and filtrates at each of temperatures 50 °C and 23 °C were taken and monitored by HPLC-UV to determine their E/Z-endoxifen ratio. The (Z)-endoxifen enriched filtrates and the E-endoxifen enriched filtrates were added back to their respective mother liquors.

[0379] HPLC-UV analyses of the samples was carried out using a Luna phenyl-hexyl column (4.6 mm x 150 mm x 3 µm of particle size). The column temperature was 40 °C and sample compartment temperature was maintained at ambient temperature. Samples were prepared by dissolving solids and filtrates at 0.2 mg/ml of sample in methanol as sample buffer. Samples were then injected into the column in an injection volume of 20 µl. Likewise, mildly acidic (pH 4.3) ammonium formate buffer/methanol in the mobile phase with gradient elution was used. Mobile phase system consisting of: Mobile Phase A (MPA) buffer was 10 mM $HCOONH_4$ with 0.03% HCOOH buffer in water, and Mobile Phase B (MBP) buffer was 10 mM $HCOONH_4$ in methanol with a gradient program used.

[0380] **Table 1**: Gradient Program

Time (m)	MPA (%)	MPB (%)
0	50	50
15	30	70
25	5	95
30	50	50

[0381] The run time was 30 m, the flow rate was 1.0 mL/m, and the delay time was 5 m. Samples were detected by UV detection at 243 nm. Retention times were typically from 12.95 to 13.20 m for (E)-endoxifen and from 14.0 to 14.33 m for (Z)-endoxifen. Relative Retention Time (RRT) for (E)-endoxifen was 0.4 to 0.9 and 1.0 for (Z)-endoxifen.

[0382] **Table 2**: Enrichment of Endoxifen (Z)- and (E)- isomers from hot slurry of E/Z-endoxifen mixture in IPA and EtOAc.

		Sample					
		1	**2**	**3**	**4**	**5**	**6**
E/Z-endoxifen ratio		51/1	1/1.8	1/5.8	51/1	1/1.8	1/5.8
E/Z-endoxifen		1 g	1 g	1 g	1 g	1 g	1 g
Solvent		**IPA** (10 X)			**EtOAc** (10 X)		
50 °C	Solid	85/1 (97.0%/1.1%)	N/A (dissolved)	1/4.2 (18.9%/**79.6**%)	≥100/1 (97.9%/0.7%)	1.9/1 (65.4%/34.2%)	1/24 (3.9%/**94.8**%)
	Filtrate	12/1 (87.0%/7.0%)	N/A (dissolved)	1/**47** (2.1%/**97.4**%)	5.4/1 (66.2%/12.3%)	1/2.4 (29.2%/**68.7**%)	1/2.5 (28.0%/**70.1**%)
23 °C	Solid	≥100/1 (98.2%/0.3%)	1/2.1 (31.8%/**67.2**%)	1/**90** (1.1%/**98.1**%)	≥100/1 (99.0%/0.4%)	1.3/1 (55.9%/43.1%)	1/6.9 (12.6%/**86.9**%)
	Filtrate	3.6/1 (70.1%/19.6%)	1/1.7 (36.5%/**60.6**%)	1/1.3 (43.4%/54.9%)	1.6/1 (37.7%/23.0%)	1/6.7 (12.6%/**84.3**%)	1/2.6 (26.2%/**84.3**%)

[0383] Results (**Table 2**) show that Z-endoxifen can be enriched using a commercial crude E/Z-endoxifen starting material from a hot slurry of the endoxifen mixtures made with IPA and EtOAc. Z-endoxifen can be purified from E/Z-endoxifen mixtures having E/Z at 1:1 and with higher Z-endoxifen levels in the mixture, for example, 1:8, and 1:5.8. Substantial Z-endoxifen enrichment was achieved in a single step using fractional crystallization method, for example with an E/Z ratio of 1:90 described herein Example 1A. (Z)-endoxifen was seen to be more soluble than (E)-endoxifen in EtOAc. (Z)-endoxifen also tended to remain in the filtrate in greater amounts in EtOAc as compared with IPA. Both solids and filtrates are useful for the preparation of (Z)-endoxifen free base. Serial enrichment of Z-endoxifen by adding filtrates back to the first filtrate (first mother liquor) can also be performed.

[0384] Similarly, E-endoxifen can be purified from E/Z-endoxifen mixture having higher E-endoxifen levels in the E/Z mixture.

[0385] ii. Similar results were obtained in experiments where an E/Z-endoxifen mixture was suspended in a hot slurry prepared with a mixture of IPA/PPW (1:1 v/v) and extracted and washed with precooled IPA/PPW (1:1) to form crystalline solids and filtrates with enriched (Z)-endoxifen.

B. Recrystallization from Solid Fraction

[0386] Serial enrichment of (Z)-endoxifen can be performed by subjecting the endoxifen mixture with E/Z-endoxifen ratio of 51:1, 1:1.8 and 1:5.6, and the solids and mother liquors obtained from the fractional crystallization to one or more rounds of recrystallization.

[0387] The (Z)-endoxifen can be enriched in substantially purified form from crude E/Z-endoxifen mixtures, (Z)-enriched crystalline solids and (Z)-enriched mother liquors by recrystallization with solvents such as ethanol, ethyl acetate/n-heptane, Acetone/MTBE, IPA, IPA/PPW, and the like under the conditions as described herein.

[0388] *Ethanol*. Crystalline solids obtained from E/Z-endoxifen hot IPA slurry mixture above were used to obtain further purified Z-endoxifen. After cooling to 23 °C, the solid fractions of sample 2 (80 g) and sample 3 (79 g) of **Table 2** above were combined and recrystallized using 1000 mL (1L) EtOH. The ethanol mixture was heated to reflux. The dissolution point was at 75 °C. The heated solution was filtered using a cellulose filter (pore size 0.5 µm) to remove foreign impurities such as cotton fibers by polish filtration. The filtrate solution was then stirred initially at 70 °C for 30 minutes. The solution was then cooled to 0 °C – 5 °C and stirred continually for 5 h at 0 °C – 5 °C. The solution was filtered again. The crystals on the filter were washed with 200 mL of EtOH.

[0389] Results show that solid crystals of endoxifen had E/Z ratio of ≥1/100 (0.22%/**99.48**%) and endoxifen in the filtrate had E/Z ratio of 1/5.9 (13.93%/**82.48**%) when recrystallized with EtOH. HPLC analysis of at least 3 different experiments conducted by this method showed that (Z) endoxifen retention time was 14.00 m, E-endoxifen retention time was 13.14 m. (Z)-endoxifen levels ranged from 97% to 99.48% while (E)-endoxifen levels ranged from 0.22% to 2.14%. Other impurities were <1%.

[0390] *Ethyl Acetate/n-heptane*. Feasibility of recrystallization with EtOAc/n-heptane was studied as described below.

[0391] 5 g Endoxifen (E/Z ratio 1/5.8) was added to EtOAc/n-heptane (140 mL, 1/1 v/v) and heated to reflux (~82 °C) while stirring overnight to obtain a clear solution. The cloud point of the mixture was 30 °C. The mixture was then cooled to room temperature to precipitate the product and filtered. After isolation as described above, endoxifen of the solid product was determined by HPLC to have an E/Z ratio of 1/8.1 (10.9%:**88.60**%) with a product yield of 66% (3.3 g). (Z)-Endoxifen in the

filtrate was enriched with E/Z ratio of 1:3 (23.94%:**74.47**%). The recrystallization using EtOAc/n-heptane can also provide purified Z-endoxifen in ratios similar to the hot IPA slurry as shown in **Table 3**.

[0392] Table 3: Recrystallization of (Z)-endoxifen from E/Z-endoxifen mixture using EtOAc/n-heptane solvent.

Parameter		**Result**
E/Z endoxifen – E/Z ratio **1/5.8**		5 g
EtOAc/n-heptane solvent (1:1)		140 mL
Heat to dissolution		~82 °C (reflux)
Cloud point		~30 °C
Cool to RT and filtration		23 °C, 1 hr
E/**Z** ratio of the product	Solid	3.3 g, 1/8.1 (10.90%/**88.60**%)
	Filtrate	1/3.0 (23.94%/**72.47**%)

[0393] *Acetone/MTBE.* 0.5 g Endoxifen (E/Z ratio 1/1.8) was added to Acetone (10 v; 5 mL) solvent, and antisolvent MTBE (9 mL) was added to the solution and heated to reflux (~82 °C) while stirring overnight to obtain a clear solution. The cloud point of the mixture was ~22 °C. The mixture was then cooled to room temperature to precipitate the product and filtered. Endoxifen in the solid product was determined by HPLC to have an E/Z ratio of 39/1 while the filtrate was enriched with (Z)-endoxifen with E/Z ratio of 1:2.6. Acetone/MTBE solvent system is useful to separate E-endoxifen to solid from the (Z)-endoxifen in the filtrate.

C. Recrystallization from Mother Liquor

[0394] Purified (Z)-endoxifen can be recovered from mother liquor enriched with (Z)-endoxifen as shown in the following **Tables 4** and **5**.

[0395] i. Starting material of crude E/Z-endoxifen mixture can be dissolved in a first solvent, ethyl acetate, to form a first mother liquor from which (Z)-endoxifen can be recovered by a second step of addition of a second solvent such as n-heptane or ethanol as shown in **Table 4**.

[0396] Table 4. Recrystallization of Z-endoxifen

Parameter	**Results**	
	Lot Number	
	1	**2**
E/Z-endoxifen (**E/Z = 1/1.8**)	5 g	10 g
EtOAc (First solvent)	50 mL	50 mL
Heat to dissolution	~68 °C	~78 °C (reflux)
Cloud Point°	~33 °C	~38 °C
Cool to RT and filtration	23 °C, 1 h	23 °C, 1 h

E/Z ratio of product	Solid	0.87g, 8.5/1 (**89.37**%/10.49%)	1.53 g, 1/1 (49.32%/49.80%)
	Filtrate	1/**3.8** (20.13%/**76.86**%)	1/ **2.6** (27.29%/**70.09**%)
Filtrate concentration Heat to dissolution		To 5 mL, 25 mL ~68 °C	To dryness ~68C
Add solvent/anti-solvent (second solvent)		**n-heptane**, 40 mL, no precipitation observed	**EtOH**, 50 mL, heat to dissolution
Cool to RT and filtration		23 °C, overnight	23 °C (cloud point ~28C)
E/Z ratio of product	Solid	3.0g, 1/4.2 (18.70%/**78.95**%)	3.2 g, 1/12 (7.52%/**90.24**%)
	Filtrate	1/3.2 (21.65%/**70.35**%)	1/1.5 (39.35%/**57.76**%)

[0397] ii. (Z)-endoxifen was prepared by a process involving: a first step of dissolving crude E/Z-endoxifen mixture in a first solvent, ethyl acetate, enriching (Z)-endoxifen to first mother liquor; a second step of addition of a second solvent, IPA to form crystalline (Z)-endoxifen and a second mother liquor; and a step of addition of a third solvent ethanol to recrystallize and recover (Z)-endoxifen from the second mother liquor.

[0398] Briefly, endoxifen (E/Z = 1/1.8, 30 g) and (E/Z = 1.2/1, 50 g non-GMP) was dissolved in EtOAc 300 mL and 500 mL respectively, heated to dissolution (~70 °C). The mixture was then cooled to 25 °C while stirring overnight for precipitation. The suspension was filtered and E/Z ratio of solid and the filtrate was determined by HPLC.

[0399] Next, the filtrates were concentrated to dryness and IPA 230 mL and 900 mL respectively were added to form hot slurries (50 °C) while stirring. The hot slurries were continuously stirred at 50 °C overnight. The slurries were then cooled to 25 °C for 0.5 h and 1 h respectively, and filtered. Z-endoxifen in the solid and the filtrates were determined again.

[0400] The solids of each sample (14.8 g and 21.6 g) were further recrystallized from 148 mL and 220 mL EtOH by heating to dissolution at NMT 70 °C and cooling to 25 °C for 0.5 h and 1 h respectively. The samples were further cooled to 0 °C – 5 °C for 1 h and filtered. The E/Z ratio of the solid and the filtrates were again determined by HPLC. E/Z ratios of each sample and purity are provided below in **Table 5**.

[0401] **Table 5**: Recovery of (Z)-endoxifen from (Z)-endoxifen enriched mother liquor

Parameter	**Results**	
	Lot Number	
	1	**2**
E/Z-endoxifen ratio	1/1.8	1.2/1
E/Z-endoxifen amount	30 g	50 g
EtOAc	300 mL	500 mL

Heat to Dissolution		~70 °C	~70 °C
Cloud Point		~33 °C	~33 °C
Cool to RT		25 °C, 3 h	25 °C, overnight
E/Z ratio of product	Solid	4.5/1 (80.52%/17.73%)	13.5/1 (92.44/6.83%)
	Filtrate	1/5.0 (16.02%/**80.71**%)	1/6.8 (12.34%/**84.45**%)
Filtrate concentration		To remove EtOAc	Swap with IP (400 ml X 2)
Add **IPA**		230 mL	900 mL
Final Volume			250 mL
Hot Slurry		50 °C overnight	50 °C, overnight
Cool to RT and filtration		25 °C, 4 h	25 °C, 4 h
E/Z ratio of product	Solid	1/31.7 (3.0%/**95.15**%)	1.31.9 (2.94%/**93.74**%)
	Filtrate	1/1.6 (36.16%/58.78%)	1/1.7 (32.17%/55.92%)
E/Z-endoxifen for recrystallization		14.8 g	21.6 g
EtOH		148 mL	220 mL
Heat to Dissolution		~70 °C	~70 °C
Cool to RT		25 °C, 0.5 h	25 °C, 1 h
E/Z ratio of Product	Solid	-	1/76.9 (1.26%/**91.91**%)
	Filtrate	-	1/20.1 (4.57%/**91.91**%)
Cool to 0 °C-5 °C and filtration		0 °C-5 °C, 1 h	0 °C-5 °C, 1 h
E/Z ratio of product	Solid (?)	1/51.8 (1.86%/**96.31**%)	1/118.7 (0.82%/**97.30**%)
	Filtrate (?)	1/6.8 (12.72%/**86.23**%)	1/8 (10.54%/**84.66**%)
Total Yield		**31%**	**29%**

[0402] Results show that purified crystalline (Z)-endoxifen of greater than 90% can be obtained by subjecting an E/Z-endoxifen mixture to fractional crystallization with a first solvent, ethyl acetate, to form crystalline solid and a first mother liquor, subjecting the first mother liquor to crystallization with a second solvent such as hot IPA to form a second crystalline solid and second mother liquor, and then recrystallization of the solids from a third solvent such as ethanol. A yield of (Z)-endoxifen of greater than 95% is also feasible. The ratio of (E)/(Z)-endoxifen can be improved from ~1.2:1 and 1:1.8 to 1:51 to over 1:118. The impurity profile of (Z)-endoxifen was analyzed by an HPLC method as described above and was found to be less than <2%. Retention time of (Z)-endoxifen and (E)-endoxifen were 14.19 m and 13.2 m respectively.

Example 2: ***Reequilibriation of (E)-endoxifen-rich E/Z-mixture***

[0403] (E)-endoxifen-rich E/Z-endoxifen mixture is also useful for the preparation Z-endoxifen free base (in addition to being useful for the preparation of purified (E)-endoxifen). (E)-endoxifen-rich E/Z-endoxifen mixture is reequilibriated from a E/Z ratio of ≥1.5:1 (for example, E/Z ratio of 51:1)

to about ~1:1 mixture. The present disclosure embraces the idea that reequilibration may be performed with a starting E/Z-endoxifen mixture having any E/Z ratio, such as 99:1 to 1:99. Such reequilibration is useful for preparation of stable (E)/(Z)-endoxifen ~1:1 mixture as well as further enrichment and purification of Z-endoxifen free base as described in Example 1 above.

[0404] Briefly, (E)-endoxifen is converted to (Z)-endoxifen by dissolving crude E/Z-endoxifen in an inert solvent such as acetonitrile/water (8:1) or dichloromethane in the presence of an acid such as hydrochloric acid, trichloroacetic acid or trifluoroacetic acid. The reaction mixture with ACN/PPW was stirred at 60 °C for 1 hour while the reaction mixture with dichloromethane and TFA was stirred at RT for 1 hour. After work up was performed as described in **Table 6**, the E/Z ratio of the product was determined to be E/Z-endoxifen (ratio about 1:1) with a purity greater than 90%.

[0405] **Table 6**: Reequilibrium of E/Z-endoxifen (E/Z ratio 51/1) to E/Z ratio of about 1:1

Parameter	**Results**	
	Sample	
	1	**2**
E/Z-endoxifen **(E/Z ratio = 51/1)**	0.5 g (off-white powder	0.5 g (off-white powder)
Solvent	**ACN/PPW** = 8/1, 5 mL (white slurry)	**CH_2Cl_2**, 5 mL (White slurry)
Acid	6N HCl, 5 mL	TFA, 5 mL
Stir	~60 °C, 6 h (Pink solution to clear solution)	~23 °C, 1 h (orange clear solution)
Work up	Quench with saturated solution of $NaHCO_3$, wash the organic layer with brine and organic layer is evaporated to dryness	Quench with saturated solution of $NaHCO_3$, wash the organic layer with brine and organic layer is evaporated to dryness
Product	Beige solid	Off-white solid
E/Z ratio	~1/1 (49.28%/47.70%)	~1.3/1 (54.51%/41.9%)
Purity	96.98%	96.20%

Example 3: *Purification of (E)-endoxifen*

[0406] (E)-endoxifen was similarly purified by recrystallization in EtOH (500 mL) by heating the reaction mixture to NMT 70 °C to get a clear solution, cooled to 0 °C – 5 °C to precipitate the product. After purification by methods described herein, 38.1 g of (E)-endoxifen was obtained in 76% yield with 97.6% purity.

Example 4: *Scale up*

[0407] Synthetic and purification methods disclosed herein also are useful in scaling up the preparation of (Z)-endoxifen for making industrial drug product dosage forms, for example, oral,

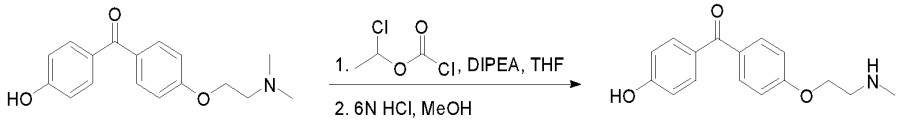
transdermal/topical, nasal, intraductal parenteral dosage forms, for use clinical use in subjects. Feasibility studies of crystallization using 5 g, 100 g, and 110 g of E/Z-endoxifen mixture, compounds of Formula (III) at an E/Z ratio of 1/5.8 were performed by suspending the E/Z-endoxifen mixtures in 10x volume of IPA and heated to 50 °C and stirred for 4 h at 50 °C. The samples were filtered using a cellulose filter pore size 0.5 µm and the E/Z ratio was determined in the solids. Following filtration, the samples were cooled to 23 °C and stirred continuously for 4 h at 23 °C. The samples were filtered again. Solids and the filtrates were monitored for (E)-endoxifen and (Z)-endoxifen levels by HPLC as described above and the results are provided below in **Table 7**.

[0408] Table 7. Scale up Preparation of (Z)-endoxifen

Parameter		**Results**		
		Sample		
		1	**2**	**3**
E/Z-endoxifen ratio 1/5.8		5 g	100 g	110 g
IPA (10 X)		50 mL	1000 mL	1100 mL
50 °C	Solid	1/20 (4.71%/**94.50**%)	1/22 (4.25%/**94.88**%)	1/16 (5.85%/**93.24**%)
	Filtrate	1/3.1 (26.54%/72.23%)	1 /2.2 (30.62%/67.52%)	1/2.3 (29.94%/68.04%)
Cooling to 23 °C stirring for 4 h	Solid	1/78 (1.26%/**97.69**%)	1/78 (2.14%/**97.24**%)	1/74 (1.32%/**98.12**%)
	Filtrate	1/1.1 (50/0.75%/47.1%)	1.1/1 (51.47%/45.88%)	1.2/1 (53.03%/43.81%)

[0409] Results show that Z-endoxifen can be obtained from an E/Z-endoxifen mixture from IPA solvent at concentrations higher than ≥ 90% as crystalline solid as well as ≥ 65% (Z)-endoxifen free base in the filtrate. IPA is thus useful as a first solvent, or second solvent or both.

Example 5: ***Industrially Scalable Preparation of [4-[2-(methylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone)***

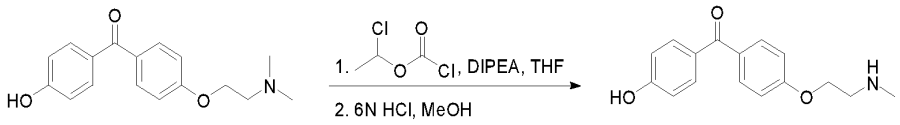


(I) (II)

[0410] A suitable 10L reactor was charged with starting material [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone, the compound of Formula (I) (0.5 kg, 1.0 equiv.), DIPEA (1.5 kg, 6.65 equiv., 3.0 wt./wt.) and tetrahydrofuran (5 L, 10 vol./wt., 8.9

wt./wt.) under N_2 atmosphere. 1-Chloroethyl chloroformate (1.7 kg, 6.65 equiv., 3.3 wt./wt.) was added slowly while maintaining the internal temperature at NMT 20 °C. The mixture was heated to reflux and stirred at reflux for NLT 12 hr. The mixture was evaporated under reduced pressure at NMT 75 °C until the volume reached the lowest agitateable volume. Methanol (2.5 L, 5 vol./wt., 4.0 wt./wt.) was added slowly and the mixture was distilled under reduced pressure at NMT 75 °C until the volume reached the lowest agitateable volume. Methanol (2.5 L, 5 vol./wt., 4.0 wt./wt.) was added and the mixture was distilled under reduced pressure at NMT 75 °C until the volume reached the lowest agitateable volume. Methanol (2.5 L, 5 vol./wt., 4.0 wt./wt.) was once again added and the mixture was further distilled under reduced pressure at NMT 75 °C until the volume once again reached the lowest agitateable volume. Methanol (2 L, 4 vol./wt., 3.2 wt./wt.) and 6N HCl (2 L, 4 vol./wt., 4.0 wt./wt.) were added to the mixture and the mixture was heated to reflux. The mixture was stirred at reflux for NLT 12 hr. After reaction completion, the mixture was evaporated under reduced pressure at NMT 75 °C until most of MeOH was removed. The mixture was cooled to 25±5 °C and 8N NaOH (2.5 L, 5 vol./wt., 5.0 wt./wt.) was added slowly until the pH of the mixture was 11-12. The mixture was stirred at 0–5 °C for NLT 2 hr. The mixture was filtered and washed with H_2O (1 L, 2 vol./wt.) and ethyl acetate (1 L, 2 vol./wt., 1.8 wt./wt.). The wet cake was dried at NMT 50 °C under reduced pressure to afford (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl)methanone, the compound of Formula (II). **Yield: 297 gm, 63%; Purity: 100%** ***(Expected Yield – 60 – 90%)***

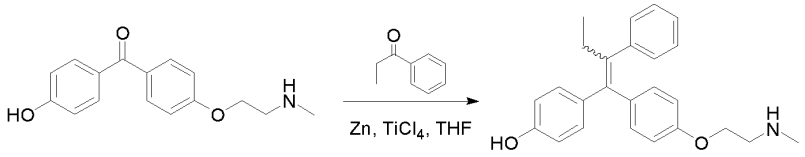
Example 6: ***Industrially Scalable Preparation of [4-[2-(methylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone)***



[0411] A suitable 2 L reactor was charged with starting material [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone, the compound of Formula (I) (70 gm, 1.0 equiv.), N-Ethyldiisopropylamine (126 gm, 4.0 equiv., 1.8 wt.) and tetrahydrofuran (700 mL, 10.0 vol., 8.9 wt.) under N_2 atmosphere. The mixture was heated to NLT 60 °C and 1-chloroethyl chloroformate (140 gm, 4.0 equiv., 2.0 wt.) added. The mixture was heated to reflux and stirred for NLT 12 hr. The mixture was concentrated until the volume reached 3 vol. Methanol (350 mL, 5.0 vol., 4.0 wt.) was added slowly and the mixture was concentrated until the volume reached 3 vol. (210 mL). Next, methanol (350 mL, 5.0 vol., 4.0 wt.) was added and the mixture was concentrated until the volume reaches 4 vol. (280 mL). 6N HCl (280 mL, 4.0 vol., 4.0 wt.) was added and the

mixture was heated to reflux. The mixture was stirred at reflux for NLT 12 hr. After reaction completion, the mixture was concentrated until the volume reaches ~4 vol. (280 mL). The mixture was cooled to ambient temperature, and 8N NaOH (NLT 350 mL, 5.0 vol., 5.0 wt.) was added slowly until the pH of the mixture is NLT 13. Ethyl acetate (280 mL, 4.0 vol., 3.6 wt.) was added to the mixture for extraction. After phase separation, to the aqueous layer was added 6N HCl (NLT 42 mL, 0.6 vol., 0.6 wt.) until the pH was 8-10. The mixture was cooled to 0±5 °C and stirred for NLT 2 hr. The mixture was filtered and washed with purified water (NLT 140 mL, 2.0 vol., 2.0 wt.) and ethyl acetate (NLT 140 mL, 2 vol., 1.8 wt.). The wet cake was dried at NMT 60 °C under reduced pressure to afford (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl)methanone, the compound of Formula (II). **Yield: 55.2 gm, 83%; Purity: 100%** ***(Expected Yield – NLT 70%)***.

Example 7: ***Industrially Scalable Preparation of E/Z-endoxifen mixture in a McMurry Reaction***



(II) (III)

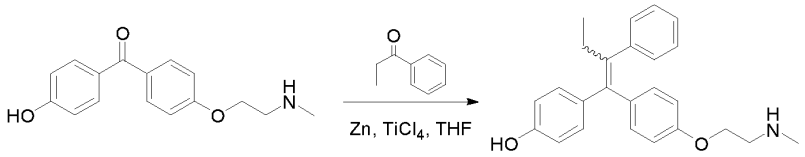
[0412] A suitable 10 L reactor was charged with Zn powder (0.27 kg, 4.0 equiv., 0.9 wt./wt.) and tetrahydrofuran (1.5 L, 5 vol./wt., 4.4 wt./wt.) under N_2 atmosphere. $TiCl_4$ (0.42 kg, 2.0 equiv., 1.4 wt./wt.) was added slowly while maintaining the internal temperature at NMT 15 °C. The reaction was heated to reflux and stirred at reflux for NLT 2 hr. A suspension of (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl)methanone, the compound of Formula (II) obtained from Step 1, (0.297 kg, 1.0 equiv.) and propiophenone (0.21 kg, 1.5 equiv., 0.7 wt./wt.) in tetrahydrofuran (3.0 L, 10 vol./wt., 8.9 wt./wt.) was added and the reflux was continued for NLT 8 hr. The mixture was cooled to 20-30 °C and added into 25% ammonium chloride (5.9 L, 20 vol./wt., 20 wt./wt.)/silica (diatomaceous earth/silicon dioxide; tradename Celite® S) available from Sigma Aldrich (0.3 kg, 1.0 wt./wt.) mixture. The mixture was filtered and washed with tetrahydrofuran (0.9 L, 3 vol./wt., 2.7 wt./wt.).

[0413] The mixture was settled for phase separation. The organic layer was collected and the aqueous layer was washed with tetrahydrofuran (0.9 L, 3 vol./wt., 2.7 wt./wt.). The organic layer was again collected and combined with the first organic layer. The combined organic layer was washed with 40% K_2CO_3 (1.2 L, 4 vol./wt., 5.6 wt./wt.). The organic layer was concentrated at NMT 75 °C under reduced pressure until the volume reached the lowest agitateable volume. Ethyl acetate (1.5 L, 5 vol./wt., 4.5 wt./wt.) was added and the mixture was distilled under reduced

pressure at NMT 75 °C until the volume reached the lowest agitateable volume. Ethyl acetate (1.5 L, 5 vol./wt., 4.5 wt./wt.) was added and the mixture was distilled under reduced pressure at NMT 75 °C until the volume reached 5 vol. (1.5 L). The mixture was heated to dissolution and n-heptane (3.0 L, 10 vol./wt., 6.8 wt./wt.) was added. The mixture was cooled to 0±5 °C and stirred at 0±5 °C for NLT 2 hr. The mixture was filtered and the residue was washed with ethyl acetate /n-heptane=1/2 (v/v, 1.5 L, 5 vol./wt., 3.7 wt./wt.). The residue wet cake was dried under reduced pressure at NMT 60 °C to afford a mixture of (Z)-endoxifen and (E)-endoxifen, (E/Z)-4-[1-[4-[2-(Methylamino)ethoxy]phenyl]-2-phenyl-1-buten-1-yl]-phenol, compounds of Formula (III). Yield: 176 g, 42%; Purity: 81.96%. E/Z ratio: **3.1:1** (Expected yield – 40 – 60%).

[0414] A suitable 10 L reactor was charged with the above (E/Z)-endoxifen (0.250 kg, 1.0 wt.), isopropanol (1.25 L, 5 vol./wt., 3.9 wt./wt.) and purified water (1.25 L, 5 vol./wt., 5.0 wt./wt.). The mixture was heated to 70±5 °C and stirred at 70±5 °C for NLT 2 hr. The mixture was cooled to 0±5 °C and stirred at 0-5 °C for NLT 2 hr. The mixture was filtered and washed with pre-cooled isopropanol/ purified water=1/1 (0.5 L, 2 vol./wt., 3.6 wt./wt.). The residue wet cake was dried at NMT 60 °C to afford a mixture of (Z)-endoxifen and (E)-endoxifen, (E/Z)-4-[1-[4-[2-(Methylamino)ethoxy]phenyl]-2-phenyl-1-buten-1-yl]-phenol, compounds of Formula (III). Yield: 105 g, 41%; Purity: 96.79%. E/Z ratio: **48.6:1** (Expected yield – 40 – 60%).

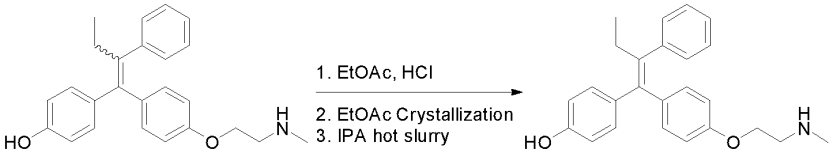
Example 8: ***Industrially Scalable Preparation of E/Z-endoxifen mixture in a McMurry Reaction***



[0415] To a suitable reactor was charged zinc powder (10 gm, 4.0 equiv., 1.0 wt.) and tetrahydrofuran (50 mL, 5.0 vol., 4.3 wt.) under N_2 atmosphere. Titanium(IV) chloride (14 gm, 2.0 equiv., 1.4 wt.) was added slowly while maintaining the internal temperature at NMT 45 °C. The reaction was heated to 65±5 °C and stirred for NLT 2 hr. A suspension of (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl)methanone, the compound of Formula (II) obtained from Example 5, (10 gm, 1.0 equiv.) and propiophenone (5 gm, 1.0 equiv., 0.5 wt.) in Tetrahydrofuran (100 mL, 10.0 vol., 8.5 wt.) was added to the above mixture and stirred at 65±5 °C for NLT 8 hr. The mixture is cooled to NMT 30 °C and 40% K_2CO_3 (20 mL, 2.0 vol., 2.0 wt.) is added. The mixture was stirred for NLT 1 hr. The mixture was filtered and washed with Me-THF (40 mL, 4.0 vol., 3.5 wt.). The filtrate was added to 40% K_2CO_3 (30 mL, 3.0 vol., 3.0 wt.) and stirred for NLT 30 min. The mixture was filtered and washed with Me-THF (20 mL, 2.0 vol., 1.7 wt.). The filtrate was settled for phase

separation and the organic layer is concentrated until the volume reached 3 vol. (30 mL). The mixture was extracted with 1N NaOH (100 mL, 10.0 vol., 10.0 wt.) and the organic layer was discarded. The aqueous layer was added sodium chloride (1 gm, 0.10 wt.) and then extracted 4 times with Me-THF (50 mL, 5.0 vol., 4.3 wt.). The 4 organic layers are combined and concentrated until the volume reached 5 vol. The mixture is extracted with 20% NaCl (50 mL, 5.0 vol., 5.0 wt.). The organic layer was added isopropanol (50 mL, 5.0 vol., 3.9 wt.) and the mixture was concentrated until the volume reached 3 vol. isopropanol (50 mL, 5.0 vol., 4.5 wt.) was added and the mixture is concentrated until the volume reached 3 vol. (30 mL). The mixture was heated to 65±5 °C and n-Heptane (120 mL, 12.0 vol., 8.2 wt.) was added. The mixture was cooled to NMT 5 °C and stirred at NMT 5 °C for NLT 2 hr. The mixture was filtered and washed with n-Heptane (50 mL, 5 vol., 3.4 wt.). The wet cake was dried at NMT 70 °C under reduced pressure to afford a mixture of (Z)-endoxifen and (E)-endoxifen, (E/Z)-4-[1-[4-[2-(Methylamino)ethoxy]phenyl]-2-phenyl-1-buten-1-yl]-phenol, compounds of Formula (III). Yield: 6.7 g, 45%; Purity: **96.79%**. E/Z ratio: **48.6:1** (Expected yield – NLT 30%).

Example 9: ***Industrially Scalable Enrichment of Z-Endoxifen***



(III) (IV)

[0416] A suitable reactor was charged with the mixture of (Z)-endoxifen and (E)-endoxifen, compounds of Formula III, (0.105 kg, 1.0 wt.) and first solvent, ethyl acetate, (1.1 L, 10 vol./wt., 9.0 wt./wt.). The mixture was cooled to 0-5 °C and 6N HCl (0.3 L, 3 vol./wt., 3.0 wt./wt.) was added slowly to the mixture. The mixture was heated to 60±5 °C and stirred at 60±5 °C for NLT 6 hr. The mixture was cooled to 0±5 °C and 8N NaOH (0.3 L, 3.0 vol./wt., 3.0 wt./wt.) was added slowly until the pH of the mixture was ≥ 12.

[0417] The mixture was settled for phase separation, the organic layer was collected and the aqueous layer was washed with the first solvent, ethyl acetate (0.5 L, 5 vol./wt., 4.5 wt./wt.). The organic layer was collected. The combined organic layers were washed with 20% NaCl (0.3 L, 3 vol./wt., 3.0 wt./wt.). The organic layer was treated with activated carbon (charcoal) (0.005 kg, 0.05 wt.) and stirred at 50±5 °C for NLT 1 hr. The mixture was filtered through a bed of diatomaceous earth/silica (Celite® S) and washed with ethyl acetate (0.5 L, 5 vol./wt., 4.5 wt./wt.). The filtrate was concentrated at NMT 75 °C until the volume reached 10 vol. (1.1 L). The mixture was cooled to

0-5 °C and stirred at 0-5 °C for NLT 2 hr. The mixture was filtered and the filtrate was collected. The filtrate was concentrated at NMT 75 °C until the volume reached the lowest agitateable volume.

[0418] A second solvent, isopropanol, (1.1 L, 10 vol./wt., 7.9 wt./wt.) was added and the mixture was concentrated at NMT 75 °C until the volume reached the lowest agitateable volume. Isopropanol (1.1 L, 10 vol./wt., 7.9 wt./wt.) was again added and the mixture was concentrated at NMT 75 °C until the volume reached the lowest agitateable volume. Isopropanol (1.1 L, 10 vol./wt., 7.9 wt./wt.) was added and the mixture was concentrated at NMT 75 °C until the volume reached 5 vol. (0.5 L). The suspension was stirred at 50±5 °C for NLT 6 hr. The mixture was cooled to 20±5 °C and stirred at 20±5 °C for NLT 4 hr. The mixture was filtered and washed with isopropanol (0.2 L, 2 vol./wt., 1.6 wt./wt.). The wet cake was dried at NMT 60 °C to afford purified (Z-endoxifen) solid compound of Formula (IV) as an off-white solid. Yield: 39.5 g, 36%, (E)/(Z) ratio: **1/12.2**; Purity (Z): **89.59%** by HPLC, Expected Yield (20-40%).

[0419] A suitable 1 L reactor was charged with the above Z-endoxifen (39 g) solid compound of Formula (IV) and a third solvent, isopropanol (390 mL, 10 vol./wt.). The suspension was stirred at 50±5 °C for NLT 6 hr. The mixture was cooled to 20±5 °C and stirred at 20±5 °C for NLT 4 hr. The mixture was filtered and washed with isopropanol (78 mL, 2 vol./wt.). The wet cake was dried at NMT 60 °C to afford purified (Z-endoxifen) solid compound of Formula (IV) as an off-white solid. Yield: 25 g, 61%, (E)/(Z) ratio: 1/55.1; Purity (Z): **95.81%**, Expected Yield (50-70%).

[0420] In this manner, polymorph Form I of endoxifen was prepared. XRPD patterns for two batches of the resultant polymorph are provided in **Figs. 9** and **10**. The XRPD peaks from **Figs. 9** and **10** are provided in **Table 8**.

[0421] **Table 8**: XRPD peaks from **Figs. 9** and **10**.

Fig. 9	
Peak Position (°2θ)	**Relative Intensity (%)**
7.1	15
9.3	22
12.4	8
14.2	26
15.2	14
16.0	20
16.8	58
17.1	100
18.2	40
18.6	15
18.9	12

Fig. 10	
Peak Position (°2θ)	**Relative Intensity (%)**
7.1	8
9.3	13
12.3	4
14.2	16
15.2	10
16.0	14
16.8	49
17.1	100
18.2	35
18.6	8
18.8	8

19.8	14
20.9	32
21.3	24
21.7	53
22.5	15
23.2	19
24.3	30
25.3	15
26.5	13
26.8	20
28.0	9
29.0	9

19.9	6
20.9	31
21.3	19
21.8	55
22.5	9
23.2	9
24.4	29
25.3	12
26.5	11
26.9	23
28.0	7
29.0	9

Example 10: ***Industrially Scalable Enrichment of ~1:1 E/endoxifen/Z-Endoxifen Mixture***

[0422] A suitable reactor was charged with the mixture of (Z)-endoxifen and (E)-endoxifen, compounds of Formula III, (0.420 kg, 1.0 wt.) and ethyl acetate (4.2 L, 10 vol./wt., 9.0 wt./wt.). The mixture was cooled to 0-5 °C and 6N HCl (1.3 L, 3 vol./wt., 3.0 wt./wt.) was added slowly. The mixture was heated to 60±5 °C and stirred at 60±5 °C for NLT 6 hr. The mixture was cooled to 0±5 °C and 8N NaOH (1.3 L, 3.0 vol./wt., 3.0 wt./wt.) was added slowly until the pH of the mixture was ≥ 12.

[0423] The mixture was settled for phase separation, the organic layer was collected and the aqueous layer was washed with ethyl acetate (2.0 L, 5 vol./wt., 4.5 wt./wt.). The organic layer was collected. The combined organic layers were washed with 20% NaCl (1.3 L, 3 vol./wt., 3.0 wt./wt.). The organic layer was treated with activated carbon (charcoal) (0.02 kg, 0.05 wt.) and stirred at 50±5 °C for NLT 1 hr. The mixture was filtered through diatomaceous earth/silica (Celite® S) bed and washed with ethyl acetate (2.0 L, 5 vol./wt., 4.5 wt./wt.). The filtrate was concentrated at NMT 75 °C until the volume reached 5 vol. (2.0 L). The mixture was heated to reflux and then cooled to 50±5 °C. n-Heptane was added slowly at 50±5 °C. The mixture was cooled to 0±5 °C and stirred at 0±5 °C for NLT 2 hr. The mixture was filtered and washed with EtOAc/n-Heptane=1/2 (v/v). The wet cake was dried under reduced pressure at NMT 60 °C to afford substantially pure ~1:1 E/Z-endoxifen. [Yield: 106 g, 25%; (E)/(Z) ratio: 1.1/1; Purity (E/Z): 97.94%, Expected Yield (20-40%)].

[0424] In this manner, polymorph Forms II and III of endoxifen were prepared. Detailed parameters for the preparation of polymorph Forms II and III are provided in **Table 9**, and XRPD patterns are provided in **Figs. 11-13**. The XRPD peaks from **Figs. 11-13** are provided in **Table 10**

[0425] **Table 9**: Parameters for isolation of polymorph Form II and Form III

Entry	1	2	3
Reactor capacity	10 L	10 L	50 L
E/Z-endoxifen input	0.37 kg	0.17 kg	0.83 kg
6N HCl	1.1 kg (3 vol.)	0.68 kg (4 vol.)	3.32 kg (4 vol.)
Reaction time	60 °C, 6 hr	60 °C, 6 hr	60 °C, 6 hr
E/Z ratio in IPC	1.1	1.1	1.1
pH after 8N NaOH neutralization	14	13	14
NaCl extraction	20% NaCl, 1.1 kg	20% NaCl, 1.0 kg	5% NaCl, 2.5 kg
Org. layer concentrate to 5 vol.	to 1.9 L (5.1 vol.)	to 1 L (5.8 vol.)	to 4 L (4.8 vol.)
n-Heptane (10 vol.) addition at 50 °C	2.5 kg, 40 min	1.2 kg, 30 min	5.6 kg, 36 min
Agitation at 50 °C	150 rpm, 40 min	130 rpm, 1 hr	150 rpm, 2 hr
Cool to 0 °C	2 hr	4 hr	5 hr
Agitation at 0 °C	150 rpm, 2 hr	140 rpm, 6 hr	150 rpm, 6 hr
Filtration time	10 min	10 min	20 min
Drying	50 °C, 4 hr	68 °C, 18 hr	69 °C, 26 hr
E/Z ratio of API	1.1	0.92	1.1
XRPD pattern	Form II (**Fig. 11**)	Form III (**Fig. 13**)	Form II (**Fig. 12**)

[0426] Table 10: XRPD peaks from **Figs. 11, 12** and **13**.

Fig. 11	
Peak Position (°2θ)	**Relative Intensity (%)**
6.6	31
7.0	42
9.3	16
11.9	100
13.3	20
14.0	96
14.1	22
15.1	11
16.8	13
17.1	22
17.7	14
18.4	69
18.6	13
20.0	16
20.8	35
21.3	17

Fig. 12	
Peak Position (°2θ)	**Relative Intensity (%)**
6.6	33
7.0	35
9.3	24
11.9	100
13.3	27
14.0	85
14.2	34
15.1	16
16.8	12
17.1	20
17.7	15
18.4	65
18.5	17
20.0	20
20.8	46
21.3	29

Fig. 13	
Peak Position (°2θ)	**Relative Intensity (%)**
6.6	24
7.0	21
9.2	19
9.6	17
11.9	55
13.3	20
13.9	39
16.8	50
17.1	100
17.7	56
18.2	38
18.3	37
19.9	22
20.2	18
20.8	38
21.3	24

21.7	59	21.7	82	21.7	56
22.0	16	22.0	18	22.5	19
22.9	14	22.9	19	22.9	17
23.2	9	23.2	16	23.9	26
23.9	17	23.9	17	24.3	29
24.3	12	24.3	14	25.3	15
				26.8	20

Example 11: ***Stability of Z-endoxifen Free Base***

[0427] Commercially, endoxifen is available as an E/Z isomer free base mixture, as well as ≥98% (Z)-endoxifen HCl and (Z)-endoxifen citrate salts. Stability of Z-endoxifen HCl salt in aqueous and solid forms has been previously published (Elkins et al. J Pharm Biomed Anal. 2014 January; 88: 174–179). Elkins et al. provide predicted t90 values for 10% conversion of (Z)-endoxifen HCl to (E)-endoxifen in the solid state of 53 months at 25 °C/60% RH and 4.3 months at 40 °C /75% RH. Conversion is expected to be more rapid in a solution environment. In an aqueous medium, Elkins et al. provide (Z)-endoxifen HCl t90 values of 149 days at room temperature and 9 days at 45 °C. There remains a need for (Z)-endoxifen free base preparations that are sufficiently stable for preparation of pharmaceutical compositions that are suitable for administering to subjects, for example, at ambient temperatures as well as at higher temperature and humidity.

[0428] Provided herein in the present disclosure are preparations of endoxifen free base that are substantially pure, at least 90% (Z)-endoxifen free base, and stable for at least 9 months under conditions of ambient and high temperature and humidity. Stability, for the purpose of this disclosure, is defined as the continued presence of at least 90% (Z)-endoxifen in a composition for at least 6 months, and is measurable by (Z)-endoxifen conversion to (E)-endoxifen starting from the date of synthesis.

A. Accelerated 10-day Stability Study of (Z)-Endoxifen Free Base

[0429] The stability of (Z)-endoxifen free base Sample 1 of **Table 11** was studied when stored at various temperatures in solid form and in ethanol (EtOH) solution. The (E)-endoxifen and (Z)-endoxifen levels were measured on days 2, 7 and 10 following placement of 1 g aliquots of purified (Z)-endoxifen free base in 180 mL HDPE bottles under dry N_2, which were then placed in double LDPE bags. The double bagged HDPE bottles containing each sample were individually packed in aluminum foil bags and thermally sealed until they were opened for testing the stability of the samples. The (E)- and (Z)-isomers of endoxifen were monitored by HPLC as disclosed above. The purity of (Z)-endoxifen in solid form remained at about 97% at 40 °C, 60 °C, and 80 °C up to 10

days. The results of the accelerated 10 days study indicate that (Z)-endoxifen in solid form does not interconvert to (E)-endoxifen at the tested temperatures up to 10 days.

[0430] Table 11: Accelerated Stability Test of Solid (Z)-endoxifen Free Base

No.		**1**	**2**	**3**
Z-endoxifen		**1 g**	**1 g**	**1 g**
Temperature		**40 °C**	**60 °C**	**80 °C**
2 days	E/Z ratio	1/76 (1.27%/**97.45**%)	1/75 (1.30%/**97.43**%)	1/76 (1.28%/**97.42**%)
	Total Impurity	1.28%	1.27%	1.30%
7 days	E/Z ratio	1/81 (1.2%/**97.11**%)	1/83 (1.17%/**87.11**%)	1/72 (1.34%/**96.92**%)
	Total Impurity	1.69%	1.72%	1.74%
10 days	E/Z ratio	1/75 (1.29%/**97.31**%)	1/82 (1.27%/**97.48**%)	1/77 (1.27%/**97.33**%)
	Total Impurity	1.40%	1.33%	1.40%

[0431] Table 12: Accelerated Stability Study of (Z)-endoxifen Free Base Solution in Ethanol

No.		**1**	**2**	**3**	**4**
(Z)-endoxifen		0.1 g	0.1 g	0.05	0.05 g
Solvent		10 mL 99.5% EtOH	10 mL 99.5% EtOH	18 mL 70% EtOH	18 mL 70% EtOH
Concentration		10 mg/mL	10 mg/mL	2.8 mg/mL	2.8 mg/mL
Temperature		**25 °C**	**40 °C**	**25 °C**	**40 °C**
2 days	E/Z Ratio	1/71 (1.37%/97.33%)	1/57 (1.70%/96.98%)	1/46 (2.09%/96.59%)	1/21 (4.43%/94.23%)
	Total Impurity	1.3%	1.32%	1.33%	1.34%
7 days	E/Z Ratio	1/50 (1.91%/**96.37**%)	1/34 (2.82%/**95.45**%)	1/17 (5.62%**92.67**%)	1/5.5 (15.23%/**83.04**%)
	Total Impurity	1.72%	1/73%	1.71%	1.73%
10 days	E/Z Ratio	1/37 (2.58%/**96.03**%)	1/27 (3.56%/**95.10**%)	1/8.4 (10.46%/**88.20**%)	1/3.4 (22.59%/**76.09**%)
	Total Impurity	1.39%	1.34%	1.34%	1.32%

[0432] Results show that (Z)-endoxifen free base is surprisingly stable in alcoholic (for example ethanol and isopropanol (data not shown)) solutions even at elevated temperatures (40 °C) at higher concentrations over 10 days. Accelerated stability at higher temperatures are generally considered predictive of long term (at least 18 m) stability at ambient temperatures.

B. Bulk Drug Stability Study

[0433] (Z)-endoxifen free base of the instant disclosure prepared by methods disclosed herein is surprisingly stable in bulk form. For bulk stability studies, ~1 g aliquots of (Z)-endoxifen free base were placed inside individually in double LDPE bags tied with a nylon cable tie. The LDPE bags were then placed in aluminum foil bags and thermally sealed. The samples for stability were placed in tightly capped, 180 mL HDPE bottles under inert conditions (dry nitrogen) at 5 °C and 25 °C/60% RH for 12 months, and at 40 °C/75% RH for 3 months. The samples were tested for (E)-endoxifen and (Z)-endoxifen concentrations and impurities, moisture or water content by Karl Fischer titration, aerobic bacterial colony forming units and appearance at time points day 0, 10 days, 1 m and 3 m. **Table 13** below provides bulk drug stability data at 9 m on endoxifen free base at varying storage conditions.

[0434] **Table 13**: Bulk Drug Stability of (Z)-endoxifen Free Base

Endoxifen (Free Base)	**%Purity Storage (5 °C)**				**%Purity Storage 25 °C/60%RH**				**%Purity Storage 40 °C/75%RH**	
	0 m	**3 m**	**6 m**	**9 m**	**0 m**	**3 m**	**6 m**	**9 m**	**0 m**	**3 m**
(Z)-endoxifen	99.5	99.6	99.5	99.5	99.5	99.6	99.5	99.5	99.5	99.5
(E)-endoxifen	0.19	0.17	0.18	0.19	0.19	0.17	0.18	0.19	0.19	0.17
Water content (Karl Fischer)	0.06	0.05	0.05	0.05	0.06	0.05	0.06	0.07	0.06	0.07
Max Indiv. Impurity	0.11	0.10	0.11	0.11	0.11	0.11	0.11	0.11	0.11	0.11
(Z)-endoxifen USP <921≥ Plate Count (cfu g/mL)	13990				14030				13776	

[0435] Results show that solid Z-endoxifen free base is stable for at least 9 months at 5 °C and 25 °C/60% RH. Accelerated stability at high temperatures is considered to be predictive of long term (at least 18 m) stability at ambient temperatures. (Z)-to-(E) endoxifen interconversion is minimal at the storage conditions studied, water content was not more than 1% and aerobic bacterial plate count

TAC (cfu) is less than 20,000 cfu g/mL. Maximum individual impurities were determined at each time point and ranged from 0.10% to 0.11%.

Example 12: ***Characteristics of Purified Solid Z-endoxifen Free Base***

[0436] (Z)-endoxifen free base, produced by methods disclosed herein, was a white to off-white powder. The water content of such a powder was not more than 1% as determined using Method 1c (Karl Fischer titration) of USP 921. The residual solvents were measured. Methanol was not more than (NMT) 3000 ppm, tetrahydrofuran NMT 720 ppm, isopropanol, ethyl acetate, n-heptane, and ethanol were each NMT 5000 ppm.

[0437] Residue on ignition of (Z)-endoxifen was not more than 0.1% as determined by Method II of USP 281. Residue on ignition of (Z)-endoxifen ranged from 0.02% to 0.099%. In some embodiments, the residue upon ignition is not more than 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, and 0.1%. In another aspect, the heavy metals were NMT 20 ppm as tested by Method II of USP 231.

[0438] Elemental levels in solid (Z)-endoxifen free base is tested using test methods of USP 232 and USP 40.

[0439] Thus, the processes described herein and endoxifen prepared using these processes are suitable for manufacture of clinical and commercial grade (Z)-endoxifen.

[0440] *FTIR spectrum of Z-endoxifen*

[0441] (Z)-endoxifen was analyzed using Fourier Transform Infra-Red Spectroscopy (Instrument type: FT/IR4600Type A; Jasco: S/N ratio 25,000:1, Max resolution 0.7 cm^{-1}) with standard light source and a TGS detector. Infrared spectra were recorded on a FTIR spectrometer (Model FT/IR 4600 Type A; manufacturer Jasco), equipped with triglycine sulfate (TGS) detector and KBr beam splitter, using AgBr windows. About 10 mg of (Z)-Endoxifen free base was placed onto the ATR crystal, pressure was applied with the tip, and the sample spectrum was collected. Spectra were collected with a scan speed to 2 mm/sec using hydrated films. Interferograms were accumulated over the spectral range 4000–650 cm^{-1} with a nominal resolution of 0.4 cm^{-1} and 32 scans. Fig 2 shows a representative IR Spectrum of (Z)-endoxifen free base.

[0442] Figure 2 shows that purified (Z)-endoxifen has peaks at 702.0, 730.9, 794.5, 825.4, 907.3, 1027.9, 1167.7, 1238.1, 1278.6, 1508.1, 1575.6, 1607.4, 3310.2 wavelengths cm^{-1} +/- 0.4 cm^{-1}. A previously published FT/IR spectrum of free endoxifen showed peaks are at 706, 831, 1053, 1171, 1240, 1465, 1507 and 1604 wavelength cm^{-1} (Agudelo et al. PLoS ONE 8(3): e60250. doi:10.1371/journal.pone.0060250).

[0443] Table 14: Spectral Assignments for IR spectrum of (Z)-endoxifen free base

Assignment	Frequency	Strength
N-H stretching O-H stretching	3200 – 3500	weak
C=C stretching	1500 – 1680	Medium
CH2 & CH3 bending	1200 - 1500	Medium
C-N stretching C-O stretching	1000 - 1200	Medium
=C-H bending =CH2 bending	690 - 1000	Medium

Example 13: ***Oral Compositions of Z-endoxifen***

[0444] *API-in-Capsule*. ≥90% Z-endoxifen free base was prepared as disclosed above. Dry white-to-off-white powder is formulated as stable free-flowing powder and filled neat into a capsule as a Drug-in-Capsule (DIC, also called API-in-capsule, AIC) oral solid dosage form. 1 mg, 2 mg, and 4 mg of endoxifen which was at least 90% (Z)-endoxifen was filled neat in a VCaps® Plus enteric capsule using Xcellodose technology (Capsugel). AIC were of size 0, Swedish orange in color.

[0445] The VCaps® Plus enteric capsules (Capsugel) are made with gluten free, non-animal self-gelling product hypromellose (methyl and hydroxypropyl mixed ether of cellulose), with low-moisture content that is suitable for moisture-sensitive ingredients such as (Z)-endoxifen. The capsules are coated with an enteric coating designed to achieve intestinal targeting (upper GI and colon), by the method of Cole et al. (Cole et al., Int. Journal of Pharmaceutics Vol. 231 83–95, 2002). Eudragit FS D30 is used as enteric coating for colonic targeted release and Eudragit L30 D55 is used as enteric coating for upper gastrointestinal targeted release.

[0446] (Z)-endoxifen free base in the AIC is released in predominantly in the intestines (upper GI and colon) and is protected from the acidic environment in the stomach for at least 6 hours. Enteric coating of the capsule prevents the release of (Z)-endoxifen in the stomach for at least 6 hours as tested by a method of USP 711.

[0447] Enteric AIC disclosed herein is stable for at least 6 months.

[0448] *Standards and testing for microbial contamination of the oral solid dosage forms of the instant disclosure*. For formulations of the solid dosage compositions disclosed herein, as the water content is NMT 1% and water activity (Aw) is less than 0.75, testing TAC and USP indicator organism is not necessary. The publication, "Microbial Bioburden on Oral Solid Dosage Form," by Jose E. Martinez, Pharmaceutical Technology, February 2002, pages 58 to 70, is hereby incorporated by reference in its entirety.

[0449] Furthermore, since formulations of the compositions disclosed herein also have water activity of less than 0.75, then no detailed microbial testing of that need be done. Total Aerobic Plate Count (TAC) is an estimation of the total viable aerobic bacteria present in a sample of raw material, in-process material, or finished product. Samples are analyzed in accordance with the most current USP Guidelines Chapter 61 (Microbial Limits Tests).

[0450] Acceptable TAC for oral solid dosage forms (OSDFs) are established for the formulation of the inventive compositions in terms of alert and action levels, which could be 1000 cfu g/ml, and 10,000 cfu g/mL respectively. A TAC that is 20,000 cfu g/mL is considered unacceptable.

Example 14: ***Preparation of (Z)-endoxifen Salt***

[0451] (Z)-Endoxifen D-gluconate salt is prepared by mixing an ethanolic slurry of (Z)-endoxifen as the free base with an aqueous solution of D-gluconic acid, followed by hydrolyzing a 20% w/v solution of D-gluconolactone in water and heating at 70 °C for 15 to 30 min. Minimum volume of ethanol is used and 5 ml of the aqueous D-gluconic acid solution is adder per 1 g of endoxifen free base. Stirring is then continued until a clear solution is obtained. (Z)-Endoxifen D-gluconate is crystallized using the methods disclosed above in Examples 1 to 4 to provide (Z)-endoxifen D-gluconate salt.

[0452] 1 mg, 2 mg, 5 mg, 10 mg, 20 mg and 40 mg AIC enteric capsules will be prepared as described above. Similarly, 1 mg to 50 mg tablets will be prepared using (Z)-endoxifen D-gluconate salt with enteric coatings EUDRAGIT ® FS D30 and EUDRAGIT ® L30D 55 to target small intestine and colon.

[0453] **Table 15**: Exemplary Tablet

Ingredient	**wt/wt of composition**
(Z)-endoxifen D-gluconate	0.1% to 20%
croscarmellose sodium	0.5% to 15%
microscrystalline cellulose	15% to 90%
mannitol	5% to 30%
Enteric coating EUDRAGIT ® L30D 55	0.01% to 3%

Example 15: ***Placebo Controlled, Dose Escalation Safety and Pharmacokinetic Study of Oral (Z)-Endoxifen***

[0454] An objective of the study was to assess the safety and tolerability of oral (Z)-Endoxifen when administered as a topical application to the breast or orally as a capsule to healthy female

volunteers. A secondary objective was to assess the pharmacokinetics of multiple doses of oral (Z)-Endoxifen in the subjects.

[0455] Generally, healthy female volunteers aged ≥ 18 years and ≤ 65 years were enrolled. 24 participants were enrolled in 3 cohorts and will be administered study drug orally. Three dose levels of orally administered (Z)-Endoxifen were investigated in 3 cohorts. In each cohort participants were randomized to receive an oral (Z)-Endoxifen or placebo in a blinded fashion. Enteric-resistant capsules used in the study were designed as delayed release capsules to resist rupture for at least 30 minutes, but typically, for about 2 hours, under gastric conditions and then open fully in intestinal fluid (DRCaps; Capsugel, a Lonza Company, USA). Enteric-resistant (Swedish Orange size Zero (0); Capsugel, USA) DRCaps capsules manually filled with 1, 2 or 4 mg of (Z)-endoxifen neat in compliance with GMP requirements were used. Placebo capsules contained microcrystalline cellulose an inert common capsule and tablet excipient.

[0456] Each cohort enrolled 8 participants, with 6 participants receiving (Z)-Endoxifen 1 mg capsules orally at 1 mg (Cohort 1), 2 mg (Cohort 2) or 4 mg (Cohort 3) doses and 2 participants receiving matching placebo capsules. In Cohort 1 (Dose Level = 1 mg) two participants (sentinels) were dosed 24 hours prior to the remaining participants. One sentinel was dosed with (Z)-Endoxifen and the other with placebo. The remaining six participants in Cohort 1 were dosed as no safety concerns were identified in the sentinel participants. The non-sentinel participants in Cohort 1 were admitted to the clinical research facility at least one day later than the sentinels. There were no sentinels in Cohorts 2 and 3.

[0457] Participant engagement in this study was for a period of 56 days. These included a 28 day screening period, and a 7 day post treatment period for Pharmacokinetic (PK) sampling. There were two confinement periods, one at the beginning and one at the end of the dosing periods. Participants were confined to the clinical facility on Days -1 through to Day 2 and Days 21 and 22. If participants were to experience any clinically significant adverse events during the study, they would have been required to remain in the clinical facility for further observation at the discretion of the Principal Investigator (PI).

[0458] Healthy female volunteers were screened within 28 days prior to commencement of dosing. Participants were admitted to the clinical facility on Day -1 for up to 3 days. The first dose of (Z)-Endoxifen or placebo capsules was administered on Day 1. Following completion of all safety assessments and sampling for PK analyses, participants were discharged from the clinical facility on Day 2. The first dose on Day 1 was followed by a 6-day treatment free period (Days 2-7). Each participant returned to the clinical facility for PK blood draws and safety assessments during the

treatment free period on study Days 4 and 6. On Day 8 participants commenced daily administration of (Z)-Endoxifen capsules or placebo capsules for 14 consecutive days (Days 8-21). Participants were supplied with study drug capsules and asked to self administer daily. Participants visited the clinical facility on Days 11, 14 and 17, prior to dose administration, for PK blood draws and safety assessments. On the morning of Day 21 each participant returned to the clinical facility prior to dose administration and were confined to the facility until Day 22 to allow for the collection of PK blood draws and safety assessments. The Day 21 dose was the last administration of study drug. Participants were discharged from the clinical facility on Day 22 and returned for PK blood draws and safety assessments on study Days 24, 26, and 28.

[0459] Study assessments included taking the subjects medical history, including evaluation of any on-study adverse events and concomitant medication use; height and weight; physical examination; periodic vital signs (body temperature, heart rate, respiratory rate, blood pressure); periodic 12-lead ECGs. Laboratory tests included hematology, coagulation, urinalysis, serum chemistry and biomarker analysis (e.g., CYP2D6, BRCA1/2, Ki67, tamoxifen metabolites, etc.). Specific assessments to evaluate treatment safety included the following: the frequency and type of adverse events, clinical laboratory testing, 12-lead ECGs and vital signs. A modified FACT-ES® scoring questionnaire was used to assess symptomatology.

[0460] Blood draws for PK analysis were collected pre-dose (within 10 min) and 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours following study drug administration on Days 1 and 21. PK samples for all other study days were collected within 10 min prior to dose administration. PK samples were obtained during the treatment free period on Days 4 and 6. Additional, PK samples were collected during the daily dosing period on Days 8, 11, 14 and 17 (within 10 min pre-dose). PK samples following completion of treatment will be collected on Days 24, 26 and 28. AUC(inf) was measured on Day 1 blood draw samples. Steady state plasma levels were determined starting from Day 8 onwards (which served as Day 0) for this determination.

Safety and Tolerability

[0461] Safety endpoints were summarized by dose cohort, with placebos pooled across cohorts. Treatment-emergent AEs were coded using the latest version of MedDRA by System Organ Class (SOC) and Preferred Term, classified from verbatim terms. The incidence and frequency of AEs, and SAEs, were summarized by cohort according to SOC and Preferred Terms, and by severity and relationship. The duration of AEs was determined and included in listings, along with the action taken and outcome. Vital signs, ECG and safety laboratory parameters were summarized at each

scheduled time point using descriptive statistics. Post-dose assessments were compared with baseline measurements. The incidence of laboratory abnormalities was summarized. Physical examination findings were presented in listings.

[0462] Treatment-emergent AEs deemed to be related to study drug (probably or possibly) were reported in 15 of 18 subjects (83%, 41 AEs) who received (Z)-Endoxifen and in 4 of 6 subjects (67%, 20 AEs) who received placebo. Most treatment-related AEs were mild in severity, with treatment related AEs of moderate severity reported in 5 of 18 subjects (28%, 6 AEs) who received (Z)-Endoxifen and in 2 of 6 subjects (33%, 2 AEs) who received placebo.

[0463] All AEs were classified as mild (75 of 84 AEs) or moderate (9 of 84 AEs) in severity, with no AEs classified as severe. Common adverse events of tension headache, headache, abdominal pain, nausea, dysmenorrhea and fatigue were reported both in subjects who received oral (Z)-Endoxifen and subjects who received placebo. Upper respiratory infection, hot flush, abdominal distension, dry mouth, and menstruation delayed were reported only in subjects who received (Z)-Endoxifen.

[0464] There were no clear differences in safety as assessed by clinical laboratory tests, vital signs, ECG assessments, FACT-ES responses in subjects who had received either topical or oral (Z)-Endoxifen compared with those who received placebo, and no dose-related trends in these safety assessments in those subjects who received (Z)-Endoxifen.

Pharmacokinetics

[0465] Mean and individual (Z)-Endoxifen serum concentration-time curves were tabulated for each dose cohort, and presented graphically with concentration displayed on a linear and logarithmic scale. Pharmacokinetic parameters were determined for each participant and summarized by cohort using descriptive statistics (arithmetic means, standard deviations, coefficients of variation, sample size, minimum, maximum and median). In addition, geometric means was calculated for AUC and Cmax. Analyses using linear models was performed to assess dose proportionality (both after a single dose and multiple dose), time dependence and accumulation (oral multiple dose), and attainment of steady state (multiple dose).

[0466] Parameters determined for the first and last dose (Days 1 and 21) included time to maximum concentration (Tmax), maximum concentration (Cmax), area under the concentration-time curve from time 0 to 24 hours following drug administration ($AUC_{0\text{-}24h}$), terminal elimination rate constant (kel), terminal half-life ($t_{1/2}$), terminal clearance (CL/F) and volume of distribution (Vd/F). Area

under the concentration-time curve from time 0 to infinity ($AUC_{0\text{-}inf}$) was also determined for the first dose, on Day 1.

[0467] The pharmacokinetic parameters were determined using non-compartmental method(s). Descriptive statistics of pharmacokinetic parameters included mean, standard deviation (SD), and coefficient of variation (CV), minimum (min) and maximum (max). Dose related trends in pharmacokinetic parameters were assessed.

[0468] Mean and individual endoxifen serum concentration-time curves were tabulated for each dose cohort. Pharmacokinetic parameters, were determined for each participant and summarized by cohort using descriptive statistics (arithmetic means, SD, CV, sample size [N], min, max and median). In addition, geometric means were calculated for AUC and Cmax. Analyses using linear models were performed to assess dose proportionality (both after a single dose (oral) and multiple dose (topical and oral)). Statistical analysis was performed on the pharmacokinetic parameters using SAS v9.3 and Phoenix WinNonLin version 7.0 or higher.

[0469] ***Abbreviations used:***

CV	Coefficient of Variance
Tmax	time to maximum concentration
Cmax	maximum concentration,
$AUC_{0\text{-}24h}$	("AUC24hr") area under the concentration-time curve from time 0 to 24 hours following drug administration
kel	terminal elimination rate constant, and volume of
t1/2	terminal half-life
CL/F	terminal clearance
Vd/F	distribution.
$AUC_{0\text{-}inf}$	("$AUC_{0\text{-}inf}$") Area under the concentration-time curve from time 0 to infinity was also determined for the first dose, on Day 1.

[0470] A summary of serum pharmacokinetic parameters with terminal half-life of (Z)-endoxifen, terminal elimination half-life, Tmax, Cmax, and AUC are provided below in **Table 16**.

[0471] Table 16: Model Serum Pharmacokinetic Parameters

Day	**(Z)-Endoxifen Dose/Day (mg)**	**Median (Range)**	**Arithmetic Mean (CV%)**		
		T_{max} (hr)	**C_{max} (ng/mL)**	**AUC_{24hr} (hr*ng/mL)**	**$t_{1/2}$ (hr)**
Day 1	1 mg (n = 5)	6.0 (2.0 – 8.08)	9.6 (18.9%)	158 (20.3%)	41.1 (15.8%)
	2 mg (n = 6)	4.17 (3.0 – 6.0)	17.7 (23.4%)	305 (17.9%)	49.0 (26.0%)
	4 mg (n = 6)	5.08 (3.0 – 6.0)	32.5 (52.3%)	587 (53.3%)	41.6 (22.9%)
Day 21	1 mg (n = 5)	8.0 (4.0 – 6.05)	24.6 (35.0%)	458 (36.3%)	52.6 (20.8%)
	2 mg (n = 6)	4.0 (2.0 – 6.05)	50.0 (23.7%)	911 (19.7%)	43.4 (17.1%)
	4 mg (n = 6)	5.0 (2.0 – 10.0)	115.0 (49.0%)	2041 (50.4%)	45.1 (15.2%)

[0472] For once daily oral administration of the delayed-release (acid-resistant) (Z)-endoxifen capsules, there was dose-proportionality (linear dose response) in Cmax and AUC_{24hr} of endoxifen across the three dose levels used in the study. Cmax increased from 9.6 ng/mL to 32.5 ng/mL for the 1 mg to 4 mg doses on day 1 and from 24.6 ng/mL to 115.0 ng/mL on Day 21. Median Tmax by dose level on Days 1 and 21 ranged from 4 to 8 hours. The apparent terminal half life ($t_{1/2}$) by dose level ranged between 42 and 53 hours, and steady state appeared to be attained after approximately 7 days (Figure 5 – dosing at Day 8 and Css at Day 14). Time to reach maximum blood levels ranged from 4 to 8 hours (Figure 4).

[0473] Table 17: Model $AUC_{(0\text{-inf})}$: 1 mg. 2 mg, and 4 mg (Z)-endoxifen

$AUC_{(0\text{-inf})}$ hr* ng/mL		
Dose: 1 mg	Dose: 2 mg	Dose: 4 mg
441	755	736
534	954	1883
739	1242	2116
527	1489	4624
593	1009	1098
	1188	1642

[0474] Table 18A: Model Serum Concentrations (nM) Over Time by Treatment, Dose: 1 mg (Z)-Endoxifen

Statistic	Pre-dose	Day 1										Day 4 Hr 72	Day 6 Hr 120	Day 8 Pre-dose	Day 11 Pre-Dose	Day 14 Pre-dose	Day 17 Pre-Dose
		hr 0.5	hr 1	hr 2	hr 3	hr 4	hr 5	hr 8	hr 10	hr 12	hr 24						
Mean	2.68	2.68	3.75	17.1	17.1	20.3	23.6	22.0	22.5	18.2	15.0	8.03	3.75	2.68	38.5	43.4	43.4
Std Dev	0.0	1.89	2.39	2.4	1.5	3.6	4.4	6.9	6.7	5.8	3.1	1.89	1.47	0.00	8.6	22.8	19.1
CV (%)	0	71	64	14	9	18	19	32	30	32	20	24	39	0	22	53	44
Median	2.68	2.68	2.68	18.7	16.1	18.7	24.1	21.4	21.4	21.4	16.1	8.03	2.68	2.68	42.8	40.2	45.5
Min	2.68	0.00	2.68	13.4	16.1	18.7	16.1	13.4	13.4	8.03	10.7	5.35	2.68	2.68	26.8	13.4	13.4
Max	2.68	5.35	8.03	18.7	18.7	26.8	26.8	32.1	32.1	21.4	18.7	10.7	5.35	2.68	45.5	75.0	64.2
GeoMean	2.68	3.18	3.33	17.0	17.1	20.1	23.2	21.1	21.6	17.1	14.7	7.84	3.53	2.68	37.7	37.6	38.5

[0475] Table 18B: Model Pharmacokinetic Parameters by Treatment; Dose 2 mg (Z)-Endoxifen (n=6).

Mean	0.17	0.00	2.17	10.2	14.5	17.2	17.2	14.3	14.5	14.2	10.3	5.67	2.80	0.83	22.5	29.2	32.2
Std Dev	0.41	0.00	1.47	3.8	2.3	4.8	3.7	3.8	3.4	2.0	2.3	1.53	1.10	0.41	3.3	4.7	7.7
CV (%)	245%	0%	68%	37%	16%	28%	21%	26%	23%	14%	22%	28%	39%	49%	15%	16%	24%
Median	0.00	0.00	2.50	10.0	14.5	17.5	17.0	14.5	14.5	14.0	10.5	5.50	3.00	1.00	22.5	28.5	29.5
Minimum	0.00	0.00	0.00	5.00	11.0	11.0	13.0	8.00	10.0	12.0	8.00	4.00	1.00	0.00	19.0	23.0	27.0
Maximum	1.00	0.00	4.00	15.0	17.0	22.0	22.0	19.0	19.0	18.0	13.0	8.00	4.00	1.00	28.0	37.0	47.0
GeoMean	1.00		2.35	9.55	14.3	16.6	16.8	13.8	14.2	14.1	10.1	5.47	2.55	1.00	22.5	28.9	31.5

[0476] Table 18C: Model Pharmacokinetic Parameters by Treatment; Dose 4 mg (Z)-Endoxifen (n=6)

N	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	0.83	0.83	3.17	20.0	27.8	26.5	30.5	25.5	30.3	27.8	21.3	10.0	5.00	2.33	50.4	69.0	68.8
Std Dev	0.41	0.41	1.72	5.0	13.7	12.1	18.0	11.3	17.8	14.9	13.2	6.8	4.64	1.97	25.1	45.8	43.0
CV (%)	49%	49%	54%	40%	49%	45%	59%	43%	59%	53%	62%	68%	93%	84%	50%	66%	62%
Median	1.00	1.00	4.00	19.0	24.5	24.0	25.5	25.0	25.0	25.5	19.5	8.00	4.00	1.50	45.0	64.0	73.0
Minimum	0.00	0.00	1.00	11.0	14.0	14.0	14.0	13.0	13.0	11.0	8.00	4.00	1.00	1.00	23.0	3.00	1.00
Maximum	1.00	1.00	5.00	35.0	52.0	49.0	62.0	42.0	62.0	52.0	43.0	23.0	13.0	6.00	77.0	145	115
GeoMean	1.00	1.00	2.62	18.9	25.3	24.8	26.7	23.5	25.4	24.6	18.0	8.54	3.62	1.82	45.2	44.9	37.5

[0477] Table 19A: Day 1 Model Pharmacokinetic Parameters by Treatment; Dose 1 mg (Z)-Endoxifen. N= 5

Statistic	Day 1								
	Cmax (ng/mL)	Tmax (hr)	AUCTlast (hr*ng/mL)	Kel (1/hr)	Thalf (hr)	$AUC_{0\text{-}inf}$ (hr*ng/mL)	AUC24hr (hr*ng/mL)	CL/F (L/hr)	Vz/F (L)
Mean	9.6	5.62	471	0.015	46.1	567	158	1.82	119.9
Std Dev	1.8	2.21	76	0.002	7.3	110	32	0.33	27.4
CV (%)	18.9	39.4	16.2	16.2	15.8	19.10	20.8	18.4	22.9
Median	10.0	6.0	472	0.015	47.2	534	171	1.87	107.6
Min	7.0	2.0	367	0.013	37.5	441	102	1.35	102.7
Max	12.0	8.08	582	0.018	54.4	739	183	2.27	168.4
GeoMean	9.5	5.11	466	0.015	45.6	559	155	1.79	117.8

GeoCV%	19.9	58.2	16.5	16.2	16.2	19.1	24.0	19.1	20.6

[0478] Table 19B: Day 1 Model Pharmacokinetic Parameters by Treatment; Dose 2 mg

N	6	6	6	6	6	6	6	6	6
Mean	17.7	4.28	889	0.015	49.0	1195	305	1.89	130.6
Std Dev	4.1	0.96	225	0.003	12.7	256	55	0.46	34.9
CV (%)	23.4	22.5	25.3	23.3	26.0	23.1	17.9	24.1	26.7
Median	17.5	4.17	955	0.016	44.0	1099	303	1.83	118.0
Minimum	13.2	3.22	537	0.010	37.8	755	248	1.34	98.2
Maximum	22.0	6.00	1137	0.018	68.1	1489	380	2.65	194.8
GeoMean	17.3	4.19	862	0.015	47.7	1081	301	1.85	127.3
GeoCV%	24.1	22.2	28.7	25.3	25.3	24.0	18.0	24.2	24.7

[0479] Table 19C: Day 1 Model Pharmacokinetic Parameters by Treatment; Dose 4 mg

N	6	6	6	6	6	6	6	6	6
Mean	32.5	5.56	1654	0.017	41.6	2017	587	2.73	154.5
Std Dev	17.3	2.47	1047	0.004	9.5	1375	313	1.60	79.9
CV (%)	52.3	44.5	63.3	21.8	22.9	68.2	53.3	58.5	51.7
Median	29.5	5.08	1423	0.017	39.9	1763	539	2.28	130.7
Minimum	14.0	3.00	691	0.012	31.6	736	258	0.87	69.9
Maximum	62.0	10.00	3574	0.022	56.0	4624	1115	5.43	258.4
GeoMean	29.1	5.15	1424	0.017	40.7	1704	521	2.35	137.8
GeoCV%	55.7	43.6	64.4	22.8	22.9	69.1	57.8	69.1	56.6

[0480] Table 19D: Day 21 Model Pharmacokinetic Parameters by Treatment; Dose 1 mg (Z)-Endoxifen. N= 5

N	5	5	5	5	5	5	5	5
Mean	24.6	6.88	458	19.1	0.014	52.6	2.49	181.3
Std Dev	8.6	1.87	166	6.9	0.003	10.9	1.06	64.1
CV (%)	35.0	27.1	36.3	36.3	20.4	20.8	42.6	35.4
Median	29.0	8.00	527	22.0	0.014	49.3	1.90	170.1
Minimum	14.0	4.00	248	10.3	0.011	40.6	1.57	116.7
Maximum	34.0	8.42	636	26.5	0.017	65.8	4.03	286.8
GeoMean	23.3	6.64	431	17.9	0.013	51.7	2.32	173.3
GeoCV%	40.1	32.1	42.2	42.2	20.9	20.9	42.2	33.9

[0481] Table 19E: Day 21 Model Pharmacokinetic Parameters by Treatment; Dose 2 mg (Z)-Endoxifen.

N	6	6	6	6	6	6	6	6
Mean	50.0	4.01	911	38.0	0.016	43.4	2.27	139.1
Std Dev	11.9	1.80	179	7.5	0.003	7.4	0.44	22.7
CV (%)	23.7	44.9	19.7	19.7	18.9	17.1	19.4	16.3
Median	51.0	4.00	910	37.9	0.015	45.7	2.21	131.6
Minimum	35.0	2.00	716	29.8	0.014	33.0	1.70	119.6
Maximum	65.0	6.05	1177	49.1	0.021	50.8	2.79	179.4
GeoMean	48.8	3.64	897	37.4	0.016	42.8	2.23	137.7
GeoCV%	24.2	53.1	19.8	19.8	18.2	18.2	19.8	15.5

[0482] Table 19F: Day 21 Model Pharmacokinetic Parameters by Treatment; Dose 4 mg (Z)-Endoxifen.

N	6	6	6	6	6	6	6	6
Mean	115.0	5.33	2041	85.1	0.016	45.1	2.83	189.0
Std Dev	56.3	2.73	1029	42.9	0.003	6.8	2.15	156.0
CV (%)	49.0	51.2	50.4	50.4	16.6	15.0	76.0	82.5
Median	131.0	5.00	2469	102.9	0.015	45.3	1.63	105.1
Minimum	42.0	2.00	616	25.7	0.013	34.0	1.32	73.0
Maximum	178.0	10.00	3034	126.4	0.020	54.3	6.49	461.5
GeoMean	100.5	4.75	1744	72.7	0.016	44.6	2.29	147.7
GeoCV%	57.4	58.5	76.1	76.1	15.9	15.9	76.1	84.6

[0483] Table 20: Mean Ratios of Pharmacokinetic Parameters (Day21)/(Day1)

(Z)-Endoxifen Dose	**Mean Ratios of Pharmacokinetic Parameters (Day 21)/(Day1)**		
	C_{max}(Day 21)/ C_{max}(Day 1)	**AUC_{24hr}(Day 21)/ AUC_{24hr}(Day1)**	**AUC_{24hr}(Day21)/ $AUC_{0\text{-}inf}$(Day1)**
1 mg (n=5)	2.74 (SD 1.29)	3.09 (SD 1.49)	0.81 (SD 0.20)
2 mg (n=6)	2.92 (SD 0.88)	3.04 (SD 0.79)	0.85 (SD 0.20)
4 mg (n=6)	3.56 (SD 1.01)	3.47 (SD 1.08)	1.08 (SD 0.38)

[0484] The mean accumulation ratios ranged from 2.74 to 3.56 for Cmax and from 3.04 to 3.47 for AUC_{24hr} as the ratio of parameters on Day 21 compared with Day 1. There was no marked trend by dose level in clearance (Cl/F) and volume of distribution (Vd/F) for Day 1 and Day 21.

[0485] Time to maximum serum endoxifen levels is achieved by about 10 hours and that there is dose-related increase in serum endoxifen levels (**Fig. 3** and **Fig. 4**). Serum endoxifen levels ranged from about 25 nM to about 80 nM.

[0486] Pharmacokinetic assessment of pre-dose trough concentration from Day 8 to Day 21 (**Fig. 4**) showed attainment of straight line after day 14. Steady state levels of serum endoxifen appear to be being achieved by Day 7 with daily dosing. The pre-dose serum concentrations indicate little accumulation after 17 days for 4mg of (Z)-Endoxifen.

[0487] Table 21: Parameter estimates of dose linearity for endoxifen

Pharmacokinetic Parameter (log)	Analyte	Day	β Estimate	Two-sided 95% Confidence Interval	r^2
Cmax	Endoxifen	1	0.808	(0.487 – 1.130)	0.66
		21	1.055	(0.655 – 1.455)	0.68
AUC_{24hr}	Endoxifen	1	0.873	(0.548 – 1.199)	0.69
		21	1.008	(0.582 – 1.433)	0.63

[0488] **Table 22**. Comparison of (Z)-endoxifen concentrations (Oral) with published literature.

(Z)-Endoxifen Dose	Published Literature Result of Average Plasma (Z)-Endoxifen Css		Study Result of Average Serum (Z)-Endoxifen Css		% Ratio of Css Study/Literature
	ng/mL	nM	ng/mL	nM	
1 mg	12.4	33.1	19.1	51.1	154%
2 mg	18.6	49.8	38	101.7	204%
4 mg	56.8	152.1	85.1	227.9	150%
8 mg	96.8	259.2	-	-	-

Css = Average Concentration at Steady State (AUCtau/tau)

[0489] ***Published literature***

1. Wu X et al. Cancer Res. 2009 Mar 1;69(5):1722-7. PubMed PMID: 19244106

2. Ahmad A et al. Breast Cancer Res Treat. 2010 Jul;122(2):579-84. PubMed PMID:20052538

3. Ahmad A et al. J Clin Oncol 30, 2012 (suppl; abstr 3089)

4. Goetz MP et al. San Antonio Breast Conference 2013 [PD3-4]

5. Goetz MP et al. San Antonio Breast Conference 2015. [PD203]

6. Ahmad A et al. Clin Transl Sci. 2016 Jun 27. doi:10.1111/cts.12407. PubMed PMID: 27346789

7. Lee O et al. Cancer Chemother Pharmacol. 2015 Dec;76(6):1235-46

[0490] Thus, data from this study suggest that safety and tolerability of oral endoxifen is generally comparable to oral tamoxifen and that subjects administered with (Z)-endoxifen compositions have plasma endoxifen levels that are within the range that has been shown to have therapeutic effect in the adjuvant setting in women with breast cancer. (Z)-Endoxifen is rapidly absorbed and systemically available and that it displays dose proportionality in peak drug concentrations in serum (C(max)) and area under the concentration-time curve extrapolated from 0 to infinity ($AUC_{0\text{-}inf}$) over the dose range 1mg - 4.0 mg.

Example 16: *Therapeutic Treatment of Tamoxifen-Refractory Breast Cancer by Oral Administration of Z-Endoxifen Free Base*

[0491] An objective of the study is to demonstrate that stable and therapeutic (Z)-endoxifen levels can be achieved in tamoxifen-refractory patients by supplementing tamoxifen with (Z)-endoxifen. Plasma endoxifen levels will be used as a surrogate endpoint to predict clinical benefit as well as the rate of recurrence in this population and to confirm the safety and tolerability of (Z)-endoxifen administration when compared with tamoxifen.

[0492] Generally healthy subjects with early stage estrogen receptor positive breast cancer who are on adjuvant therapy of tamoxifen for at least 30 days will be enrolled for the study for up to 6 months. At least seventy-five tamoxifen-refractory breast cancer subjects will be enrolled in the study to ensure an evaluable population consists of at least 25 tamoxifen and 25 (Z)-endoxifen subjects is achieved. Additional subjects may be enrolled to achieve the desired population of tamoxifen-refractory subjects. These subjects will have been diagnosed with breast cancer and undergone mastectomy or lumpectomy.

[0493] After at least 30 days of oral tamoxifen, endoxifen plasma levels will be measured. If the endoxifen level is below 30 or 40 nM, then 1 mg of oral (Z)-endoxifen will be added to the oral tamoxifen adjuvant regimen. Additional (Z)-endoxifen doses will be added until a stable endoxifen of at least 40 nM but not more than 80 nM is achieved. The endpoint is to establish a therapeutically stable endoxifen level in the tamoxifen+endoxifen group for at least 6 months.

Example 17: ***Pre-surgical Treatment of Estrogen Receptor Positive Breast Cancer by Oral Administration of Z-Endoxifen-D-gluconate***

[0494] An objective is to determine if Z-Endoxifen-D-gluconate reduces tumor activity in pre-surgical estrogen receptor positive breast cancer patients. Upon the initial diagnosis of ER+ breast cancer, 8 patients will be assigned to one of 3 groups, where each patient will receive 1, 2, or 4 mg of (Z)-endoxifen-D-gluconate for 21 days prior to surgery.

[0495] The biomarker KI-67 levels of the tumor will be compared from the time of initial biopsy and the surgical sample will be compared to determine if one of the 3 doses results in a decrease in tumor activity.

Example 18: ***Therapeutic Treatment of Breast Cancer by Oral Administration of (Z)-Endoxifen D-Gluconate***

[0496] An objective of the study is to demonstrate that therapeutic (Z)-endoxifen levels in the subject's plasma can be achieved in tamoxifen-refractory patients initiating adjuvant breast cancer therapy. Plasma endoxifen levels will be used as a surrogate endpoint to predict clinical benefit as well as the rate of recurrence in this population and to confirm the safety and tolerability of oral (Z)-endoxifen D-gluconate administration when compared with tamoxifen.

[0497] Generally healthy subjects with estrogen receptor positive breast cancer for whom tamoxifen is indicated as part of their complete treatment regimen will be enrolled for the study for up to 6 months. At least seventy five tamoxifen-refractory breast cancer subjects will be enrolled in the study to ensure an evaluable population consists of at least 25 tamoxifen and 25 (Z)-endoxifen

subjects is achieved. Additional subjects may be enrolled to achieve the desired population of tamoxifen-refractory subjects. These subjects will have been diagnosed with breast cancer and undergone mastectomy or lumpectomy.

[0498] Immediately after mastectomy or lumpectomy, 25 subjects will be assigned to the tamoxifen group and administered daily with oral 20 mg Tamoxifen for a period of 3 months. Additional 25 subjects will be assigned to the (Z)-endoxifen group and administered daily with oral 10 mg tablet of (Z)-endoxifen D-gluconate for a period of 3 months. Blood will be drawn from each subject at day 0 (baseline), and on days 7, 14, 21, 28, 60 and 90. Plasma (Z)-endoxifen levels, hematology, chemistry, and coagulation parameters will be taken for both treatment sets on day 0 (baseline measurement), as wells as on days 7, 14, 21, 28, 60 and 90.

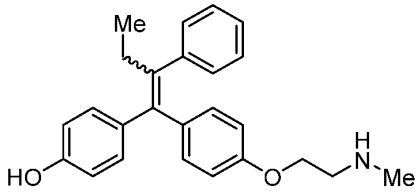
[0499] The plasma (Z)-endoxifen levels of the two treatment sets will be compared to each other. If the plasma endoxifen levels of the tamoxifen treated subjects are less than 30 nM, then those subjects will be transferred to the (Z)-endoxifen therapy group and the treatment will continue for an additional 6 months. If the plasma endoxifen levels of the tamoxifen treated subjects are above 30 nM, they will continue to be treated with tamoxifen. Bloods samples will continue to be drawn weekly until the end of the study to monitor the subjects' plasma (Z)-endoxifen levels, hematology, chemistry, and coagulation parameters. Recurrence of cancer in the subjects will be monitored and compared between the treatment groups. Safety and efficacy will be evaluated every 3 months until the end of the study.

[0500] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

CLAIMS

WHAT IS CLAIMED IS:

1. A composition comprising a crystalline form of a compound of Formula (III):



Formula (III).

2. The composition of claim 1, wherein at least 90% by weight of the compound of Formula (III) in the composition is the (Z)-isomer.

3. The composition of claim 2, wherein the crystalline form is Form I of the compound of Formula (III).

4. The composition of claim 3, wherein the crystalline form is characterized by an x-ray powder diffraction pattern comprising major peaks at 16.8 ± 0.3°, 17.1 ± 0.3° and 21.8 ± 0.3° two theta.

5. The composition of claim 4, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 16.0 ± 0.3°, 18.8 ± 0.3° and 26.5 ± 0.3° two theta.

6. The composition of claim 4 or 5, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 12.3 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.

7. The composition of claim 4, wherein the x-ray powder diffraction pattern further comprises peaks at 12.3 ± 0.3°, 16.0 ± 0.3°, 18.8 ± 0.3°, 26.5 ± 0.3°, 28.0 ± 0.3° and 29.0 ± 0.3° two theta.

8. The composition of any one of claims 3 to 7, wherein the crystalline form is characterized by an x-ray powder diffraction pattern substantially as set forth in Fig. 9 or Fig. 10.

9. The composition of any one of claims 3 to 8, wherein greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition is crystalline Form I.

10. The composition of any one of claims 3 to 9, wherein the composition comprises 0.01 mg to 200 mg of crystalline Form I.

11. The composition of claim 10, wherein the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form I.

12. The composition of claim 1, wherein the composition comprises the (E)-isomer and the (Z)-isomer of the compound of Formula (III) in an E/Z ratio between 0.9 and 1.3.

13. The composition of claim 12, wherein the E/Z ratio is about 1.1.

14. The composition of claim 12 or 13, wherein the crystalline form is Form II of the compound of Formula (III).

15. The composition of claim 14, wherein the crystalline form is characterized by an x-ray powder diffraction pattern comprising major peaks at 7.0 ± 0.3°, 11.9 ± 0.3°, 14.0 ± 0.3° and 18.4 ± 0.3° two theta.

16. The composition of claim 15, wherein the x-ray powder diffraction pattern further comprises a peak at 22.0 ± 0.3° two theta.

17. The composition of claim 15 or 16, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 6.6 ± 0.3°, 13.3 ± 0.3° and 20.0 ± 0.3° two theta.

18. The composition of claim 15, wherein the x-ray powder diffraction pattern further comprises peaks at 6.6 ± 0.3°, 13.3 ± 0.3°, 20.0 ± 0.3° and 22.0 ± 0.3° two theta.

19. The composition of any one of claims 14 to 18, wherein the crystalline form is characterized by an x-ray powder diffraction pattern substantially as set forth in Fig. 11 or Fig. 12.

20. The composition of any one of claims 14 to 19, wherein greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition is crystalline Form II.

21. The composition of any one of claims 14 to 20, wherein the composition comprises 0.01 mg to 200 mg of crystalline Form II.

22. The composition of claim 21, wherein the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form II.

23. The composition of claim 12 or 13, wherein the crystalline form is Form III of the compound of Formula (III).

24. The composition of claim 23, wherein the crystalline form is characterized by an x-ray powder diffraction pattern comprising major peaks at 11.9 ± 0.3°, 13.9 ± 0.3°, 17.1 ± 0.3° and 17.7 ± 0.3° two theta.

25. The composition of claim 24, wherein the x-ray powder diffraction pattern further comprises a peak at 25.3 ± 0.3° two theta.

26. The composition of claim 24 or 25, wherein the x-ray powder diffraction pattern further comprises at least one peak selected from 18.2 ± 0.3°, 22.5 ± 0.3° and 26.8 ± 0.3° two theta.

27. The composition of claim 24, wherein the x-ray powder diffraction pattern further comprises peaks at 18.2 ± 0.3°, 22.5 ± 0.3°, 25.3 ± 0.3° and 26.8 ± 0.3° two theta.

28. The composition of any one of claims 23 to 27, wherein the crystalline form is characterized by an x-ray powder diffraction pattern substantially as set forth in Fig. 13.

29. The composition of any one of claims 23 to 28, wherein greater than 90%, 95% or 99% by weight of the compound of Formula (III) in the composition is crystalline Form III.

30. The composition of any one of claims 23 to 29, wherein the composition comprises 0.01 mg to 200 mg of crystalline Form III.

31. The composition of claim 30, wherein the composition comprises about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of crystalline Form III.

32. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and the composition of any one of the preceding claims.

33. The composition of any one of the preceding claims, wherein the composition is formulated for oral, parenteral, topical, or intraductal delivery.

34. The composition of any one of the preceding claims, wherein the composition is formulated for oral delivery as a tablet, a caplet, a capsule, or a pill.

35. The composition of any one of the preceding claims, wherein a mean half-life of endoxifen in a subject treated with the composition is between 30 hours to 60 hours.

36. The composition of any one of the preceding claims, wherein the composition is formulated for oral delivery as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

37. The composition of any one of the preceding claims, wherein the composition is administered to a subject for the treatment or prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in the subject.

38. An oral composition comprising 1 mg to 200 mg per unit dose of the composition of any one of the preceding claims for administration to a subject in need thereof, wherein daily administration of the oral composition achieves in the subject:

a steady state plasma level of endoxifen within 7 to 21 days;

a steady state plasma level of endoxifen ranging from 25 nM to 300 nM;

a steady state plasma level of endoxifen greater than 30 nM;

maximal plasma levels of endoxifen within 2 to 10 hours after administering; or

any combination thereof.

39. The oral composition of claim 38, wherein a mean half-life of endoxifen in a subject treated with the composition is between 40 hours to 55 hours.

40. The oral composition of claim 38 or 39, wherein the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

41. The composition of any one of the preceding claims, wherein at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of endoxifen in the composition is released in the intestines.

42. The composition of any one of the preceding claims, having a mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of endoxifen of 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL.

43. A method of treating a subject in need thereof, the method comprising administering to the subject the composition of any one of claims 1 to 42.

44. The method of claim 43, wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

45. The method of claim 44, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

46. The method of any one of claims 43 to 45, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

47. The method of any one of claims 43 to 46, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

48. The method of any one of claims 43 to 47, wherein the subject is or will be treated with an SSRI drug selected from the group consisting of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone.

49. The method of any one of claims 43 to 48, wherein the composition comprises 0.01 mg to 200 mg of (Z)-endoxifen.

50. The method of any one of claims 43 to 49, wherein the subject is administered about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen daily.

51. The method of any one of claims 43 to 50, wherein a steady state plasma level of endoxifen in the subject is greater than 30 nM.

52. The method of any one of claims 43 to 51, wherein the steady state plasma level of endoxifen is achieved within 7 to 21 days of the first administration of the composition.

53. The method of any one of claims 43 to 52, wherein time to maximum plasma levels of endoxifen ranges from 2 hours to 10 hours or from 4 hours to 8 hours after administering the composition.

54. A method of treating a subject having or at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both, the method comprising administering the composition of any one of claims 1 to 42, wherein administration of the composition achieves:

a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;

a time to maximum plasma levels of endoxifen ranging from 4 hours to 8 hours after administration; and

a steady state plasma level of endoxifen greater than 30 nM.

55. The method of claim 54, wherein the hormone-dependent breast disorder and the hormone-dependent reproductive tract disorder are selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer.

56. The method of claim 54 or 55, wherein the composition comprises 0.01 mg to 200 mg of (Z)-endoxifen.

57. The method of claim 56, wherein the subject is administered about 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen.

58. The method of any one of claims 43 to 57, wherein the mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of endoxifen is 200 hr*ng/mL to 10000 hr*ng/mL, 300 hr*ng/mL to 8000 hr*ng/mL, 400 hr*ng/mL to 6000 hr*ng/mL or 700 hr*ng/mL to 6000 hr*ng/mL.

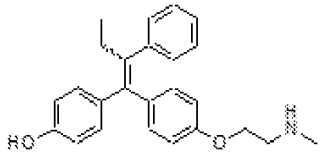
59. The method of any one of claims 43 to 58, wherein the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

60. The method of any one of claims 43 to 59, wherein at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of endoxifen in the composition is released in the intestines.

61. The method of any one of claims 43 to 60, wherein the composition is administered once a day, twice a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually.

62. An industrially scalable process for manufacturing (Z)-endoxifen, comprising the steps of:

(a) subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), represented by



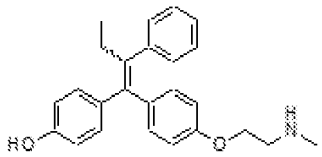
to fractional crystallization from a first solvent to form a first crystalline solid and first mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen;

(b) subjecting the first mother liquor to recrystallization from a second solvent by concentrating the first mother liquor or by swapping out the first solvent from the first mother liquor with the second solvent one or more times, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is $\geq$ 90% (Z)-endoxifen; and

(c) optionally, subjecting the second crystalline solid to recrystallization from a third solvent or chromatographic treatment one or more times to form a third crystalline solid.

63. An industrially scalable process for manufacturing the crystalline form of any one of claims 1 to 11, comprising the steps of:

(a) subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), represented by

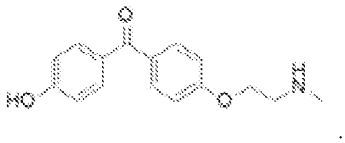


to fractional crystallization from a first solvent to form a first crystalline solid and first mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen;

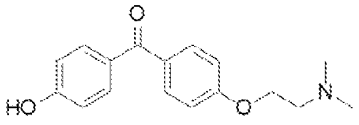
(b) subjecting the first mother liquor to recrystallization from a second solvent by concentrating the first mother liquor or by swapping out the first solvent from the first mother liquor with the second solvent one or more times, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥ 90% (Z)-endoxifen; and

(c) subjecting the second crystalline solid to recrystallization from a third solvent or chromatographic treatment one or more times to form a third crystalline solid, wherein the third crystalline solid is the crystalline form of any one of claims 1 to 11.

64. The process of claim 62 or 63, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is prepared by coupling a compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, to propiophenone mediated by a McMurry reaction via a titanium salt and a reducing agent in an inert organic solvent to form the mixture of (E)-endoxifen and (Z)-endoxifen; and wherein the compound of Formula (II) has a structure represented by



65. The process of claim 64, further comprising preparing the compound of Formula (II) by demethylating [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone, a compound of Formula (I), wherein the compound of Formula (I) has the structure



with a demethylating agent and a proton acceptor in an inert organic solvent to form the compound of Formula (II).

66. The process of any one of claims 62 to 65, wherein the first solvent is ethyl acetate, IPA, IPA/PPW, ACN, ACN/PPW or acetone.

67. The process of any one of claims 62 to 66, wherein the second solvent is IPA, IPA/PPW, acetone, ethanol, ethyl acetate, or acetone/MTBE.

68. The process of any one of claims 62 to 67, wherein the third solvent is ethanol, methanol, ethyl acetate, IPA, IPA/PPW, n-heptane, or acetone.

69. The process of any one of claims 62 to 68, further comprising pre-heating any one or more of the first solvent, the second solvent and the third solvent to a temperature ranging from 40 °C to 80 °C.

70. The process of any one of claims 62 to 69, wherein each fractional crystallization and recrystallization step independently comprises a step of distillation at 50 °C to 80 °C; and cooling the solution to a temperature ranging from 0 °C to NMT 35 °C.

71. The process of any one of claims 64 to 70, further comprising the steps of:

(a) reacting the compound of Formula (II) with propiophenone in an inert organic solvent;

(b) preparing a titanium salt and a reducing agent in an inert organic solvent; and

(c) reacting the compound of Formula (II) of step (a) with the titanium salt and a reducing agent in an inert organic solvent of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen.

72. The process of any one of claims 64 to 71, further comprising the steps of:

(a) reacting the compound of Formula (II) with propiophenone (1:0.01 to 1:5 wt/wt) in an inert organic solvent (1:1 to 1: 20 wt/wt);

(b) preparing a titanium salt (1:0.1 to 1:12 wt/wt) and a reducing agent (1:0.01 to 1:10 wt/wt) in an inert organic solvent (1:1 to 1: 20 wt/wt); and

(c) reacting the compound of Formula (II) of step (a) with the titanium salt and a reducing agent in an inert organic solvent of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen;

wherein wt/wt is with respect to compound of Formula (II).

73. The process of any one of claims 64 to 72, wherein the titanium salt is selected from the group consisting of titanium halides (such as titanium trichloride ($TiCl_3$), titanium tetrachloride ($TiCl_4$), titanium iodides, titanium bromides, and titanium fluorides), titanium(IV) trichloride isopropoxide, and titanium isopropoxide.

74. The process of any one of claims 64 to 73, wherein the reducing agent is selected from the group consisting of zinc, zirconium, vanadium, niobium, molybdenum, tungsten, aluminum, magnesium, potassium, zinc-copper couple, alkali and alkali earth metals, butylium, lithium, and lithium aluminum hydride.

75. The process of any one of claims 64 to 74, wherein the inert organic solvent is selected from the group consisting of dichloromethane, dichloroethane, chloroform, carbon tetrachloride, chlorobenzene, diethyl ether, 1,4-dioxane, tert-butyl methyl ether, tetrahydrofuran, N,N-

dimethylformamide, N-methylpyrrolidone, diglyme, nitromethane, 1,2-dimethoxyethane, pyridine, acetone, acetonitrile, benzene, o-xylene, m-xylene, p-xylene, xylenes, hexanes, cyclohexane, heptane, octane, nonane, and decane, or a combination thereof.

76. The process of any one of claims 64 to 75, wherein the preparation of the titanium salt and the reducing agent in the inert organic solvent in step (b) further comprises maintaining the temperature of the reaction at a temperature of NMT 75 °C, NMT 65 °C, NMT 55 °C, NMT 50 °C, NMT 45 °C, NMT 40 °C, NMT 35 °C, NMT 30 °C, NMT 25 °C, NMT 20 °C, or NMT 15 °C when the titanium salt is added to the reducing agent and the inert organic solvent.

77. The process of any one of claims 64 to 76, wherein the preparation of the titanium salt and the reducing agent in the inert organic solvent further comprising maintaining the temperature of the reaction at a temperature NMT 75 °C, NMT 70 °C, NMT 65 °C, NMT 60 °C, NMT 55 °C, NMT 50 °C, or NMT 45 °C when the titanium salt is added to the reducing agent and the inert organic solvent.

78. The process of any one of claims 64 to 77, wherein the preparation of the titanium salt and the reducing agent in the inert organic solvent in step (b) further comprises heating the titanium salt and the reducing agent in the inert organic solvent to a temperature ranging from 20 °C to 250 °C, from 40 °C to 70 °C, from 50 °C to 230 °C, from 50 °C to 120 °C, or from 150 °C to 200 °C.

79. The process of any one of claims 64 to 78, wherein the preparation of the titanium salt and the reducing agent in the inert organic solvent in step (b) further comprises heating the titanium salt and the reducing agent in the inert organic solvent under reflux for NLT 30 min, NLT 1 hour, NLT 2 hours, NLT 4 hours, NLT 6 hours, or NLT 8 hours under N_2 or argon.

80. The process of any one of claims 64 to 79, wherein the compound of Formula (II) of step (a) is reacted with titanium salt and a reducing agent in an inert organic solvent of step (b) under reflux to form the mixture of (E)-endoxifen and (Z)-endoxifen.

81. The process of any one of claims 64 to 80, wherein the compound of Formula (II) of step (a) is reacted with titanium salt and a reducing agent in an inert organic solvent of step (b) at a temperature ranging from 40 °C to 80 °C to form the mixture of (E)-endoxifen and (Z)-endoxifen for NLT 4 hours, NLT 6 hours, NLT 8 hours, NLT 12 hours, NLT 24 hours, or NLT 48 hours.

82. The process of any one of claims 64 to 81, further comprising a step of cooling the mixture of (E)-endoxifen and (Z)-endoxifen to a temperature ranging from 0 °C to 30 °C.

83. The process of any one of claims 64 to 82, further comprising one or more steps of:

(a) extraction of the mixture of (E)-endoxifen and (Z)-endoxifen;

(b) washing the mixture of (E)-endoxifen and (Z)-endoxifen;

(c) distillation of the mixture of (E)-endoxifen and (Z)-endoxifen; and

(d) crystallization to afford a crystalline solid mixture of (E)-endoxifen and (Z)-endoxifen.

84. The process of claim 83, wherein the extraction is carried out one or more times in MeTHF or THF.

85. The process of any one of claims 65 to 84, further comprising generating the compound of Formula (II) by demethylating the compound of Formula (I) with a demethylating agent (1:0.5 to 1:10 wt/wt) and a proton acceptor (1:0.5 to 1:10 wt/wt) in an inert organic solvent (1:1 to 1: 20 wt/wt) to form the compound of Formula (II), wherein the wt/wt ratios are with respect to the compound of Formula (I).

86. The process of any one of claims 65 to 85, wherein the proton acceptor is selected from the group consisting of carbonates, such as sodium carbonate and potassium carbonate, and bicarbonates, such as sodium bicarbonate and potassium bicarbonate, proton sponge, and DIPEA.

87. The process of any one of claims 65 to 86, wherein the demethylating agent is selected from the group consisting of N-iodosuccinamide, ethyl chloroformates (such as 1-chloroethyl chloroformate, dichloroethyl chloroformate, trichloroethyl chloroformate, α-chloroethyl chloroformate), vinyl chloroformate, cynogen bromide, diethyl azodicarboxylate, and pyridinium chloride.

88. The process of any one of claims 65 to 87, wherein the compound of Formula (I) is reacted with the demethylating agent and the proton acceptor at a temperature ranging from 20 °C to 250 °C, from 40 °C to 80 °C, from 50 °C to 230 °C, from 50 °C to 120 °C, and from 150 °C to 200 °C.

89. The process of any one of claims 65 to 88, wherein the compound of Formula (I) is reacted with the demethylating agent and the proton acceptor under reflux.

90. The process of any one of claims 65 to 89, wherein the compound of Formula (I) is reacted with the demethylating agent and the proton acceptor for NLT 5 hours, NLT 8 hours, NLT 12 hours, NLT 24 hours, NLT36 hours, NLT 48 hour or NLT 72 hours.

91. The process of any one of claims 3 or 85 to 90, further comprising one or more steps of:

(a) distillation;

(b) reaction with solvent/acid mixture;

(c) neutralization with a neutralizing agent; and

(d) drying under reduced pressure.

92. The process of claim 91, wherein the distillation step comprises one or more solvent swaps with an organic distillation solvent selected from the group consisting of ethyl acetate, alcohols, such as methanol, ethanol, n-propanol, and isopropanol, benzene, acetone, acetonitrile, toluene, dichloromethane, 1,2-dichloroethane, and chloroform.

93. The process of claim 91 or 92, wherein the solvent/acid mixture is selected from the group consisting of methanol/HCl, ethanol/HCl, propanol/HCl, isopropanol/HCl, methanol/sulfuric acid, methanol/phosphoric acid, ethanol/sulfuric acid, ethanol/phosphoric acid, propanol/sulfuric acid, propanol/phosphoric acid, isopropanol/sulfuric acid, isopropanol/phosphoric acid, methanol/acetic acid, ethanol/acetic acid, propanol/acetic acid, isopropanol/acetic acid, methanol/formic acid, ethanol/formic acid, propanol/formic acid, and isopropanol/formic acid.

94. The process of any one of claims 91 to 93, wherein neutralizing agent is sodium hydroxide, ammonium hydroxide, potassium hydroxide, or aminomethylpropanol.

95. The process of any one of claims 62 to 94, further comprising converting (E)-endoxifen to (Z)-endoxifen by reacting a mixture of (E)-endoxifen and (Z)-endoxifen to an acid (1:1 to 1:5 wt/wt) in a solvent (1:1 to 1:20 wt/wt), wherein the wt/wt ratios are with respect to compounds of Formula (III).

96. The process of claim 95, wherein the acid is HCl, TCA, or TFA.

97. The process of claim 95 or 96, wherein the solvent is acetonitrile, acetonitrile/PPW, IPA, IPA/PPW, dichloromethane, or ethyl acetate.

98. The process of any one of claims 95 to 97, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is heated with the acid in the solvent under reflux and stirred for NLT 4 hours, NLT 6 hours, NLT 12 hours, NLT 24 hours, or NLT 48 hours.

99. The process of any one of claims 95 to 98, further comprising one or more steps of:

(a) neutralization with a neutralizing agent;

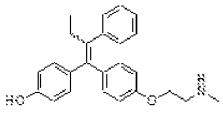
(b) extraction;

(c) one or more washes; and

(d) treatment with activated carbon.

100. An industrially scalable process for manufacturing (Z)-endoxifen, comprising the steps of:

(a) subjecting a mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III) represented by



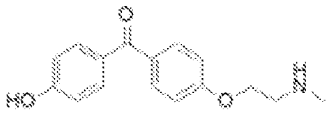
to fractional crystallization from ethyl acetate to form a first crystalline solid and first crystalline mother liquor, wherein the first mother liquor has an E/Z ratio of at least 50% higher (Z) endoxifen as compared with the E/Z ratio of the mixture of (E)-endoxifen and (Z)-endoxifen;

(b) subjecting the first mother liquor to recrystallization from the IPA or IPA/PPW (1:1 v/v) by concentrating the first mother liquor, or by swapping out the ethyl acetate from the first mother liquor with IPA or IPA/PPW one or more times, to form a second crystalline solid and a second mother liquor, wherein the second crystalline solid is ≥ 90% (Z)-endoxifen; and

(c) optionally, subjecting the second crystalline solid to recrystallization from ethanol or column chromatographic treatment one or more times to form a third crystalline solid.

101. The process of claim 99 or 100, wherein the mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), in step a is pretreated with 6N HCl and neutralized with 8N NaOH.

102. The process of any one of claims 99 to 101, wherein the mixture of (E)-endoxifen and (Z)-endoxifen, compounds of Formula (III), is prepared by coupling a compound of Formula (II), (4-hydroxyphenyl)(4-(2-(methylamino)ethoxy)phenyl) methanone, to propiophenone catalyzed in a McMurry reaction via $TiCl_4$ and Zn in THF to form the mixture of (E)-endoxifen and (Z)-endoxifen; and wherein the compound of Formula (II) has a structure represented by



103. The process of claim 102, further comprising the steps of:

(a) reacting the compound of Formula (II) with propiophenone in THF;

(b) preparing $TiCl_4$ and Zn in THF; and

(c) reacting the compound of Formula (II) of step (a) with the $TiCl_4$ and Zn in THF of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen.

104. The process of claim 102 or 103, comprising the steps of:

(a) reacting the compound of Formula (II) with propiophenone in THF (1:1 to 1:20 wt/wt);

(b) preparing a $TiCl_4$ (0.1 to 12 wt/wt) and Zn (0.01 to 1:10 wt./wt) in THF (1:1 to 1:20 wt/wt); and

(c) reacting the compound of Formula (II) of step (a) with the $TiCl_4$ and Zn in THF of step (b) to form the mixture of (E)-endoxifen and (Z)-endoxifen,

wherein wt/wt is with respect to the compound of Formula (II).

105. The process of any one of claims 102 to 104, wherein preparation of $TiCl_4$ and Zn in THF further comprises heating under reflux for NLT 2 hours under N_2.

106. The process of any one of claims 102 to 105, further comprising the steps of extractive purification, distillation, and crystallization.

107. The process of any one of claims 102 to 106, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is subjected to extractive purification comprising a step of:

(a) extraction one or more times with ammonium chloride, silicon dioxide, 40% K_2CO_3, and THF;

(b) extraction one or more times with K_2CO_3 and MeTHF;

(c) extraction one or more times with NaOH, NaCl, and MeTHF;

(d) extraction one or more times with MeTHF or THF;

(e) extraction one or more times with 20% NaCl; or

(f) a combination thereof.

108. The process of any one of claims 102 to 107, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is subjected to extractive purification comprising the steps of:

(a) extraction one or more times with 40% K_2CO_3 (1:1 to 1:10 wt/wt) and MeTHF (1:1 to 1:10 wt/wt);

(b) extraction one or more times with 1N NaOH (1:1 to 1:20 wt/wt), NaCl (1:0.01 to 1:0.5 wt/wt) and MeTHF (1:1 to 1:10 wt/wt);

(c) extraction one or more times with MeTHF (1:1 to 1:5 wt/wt); and

(d) extraction with 20% NaCl (1:1 to 1:10 wt/wt);

wherein the wt/wt is with respect to the compound of Formula (II).

109. The process of any one of claims 102 to 108, wherein the mixture of (E)-endoxifen and (Z)-endoxifen is subjected to extractive purification comprising the steps of:

(a) extraction with 25% ammonium chloride (1:10 to 1:30 wt/wt), silicon dioxide (1:0.01 to 1:5 wt/wt) and THF (1:1 to 1:5 wt/wt);

(b) one or more washes with THF (1:1 to 1:5 wt/wt); and

(c) one or more washes with 40% K_2CO_3 (1:1 to 1:10 wt/wt);

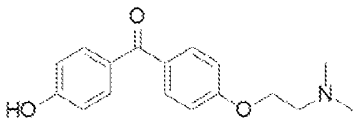
wherein the wt/wt is with respect to the compound of Formula (II).

110. The process of claim 108 or 109, wherein the step of distillation is performed 1 to 5 times with EtOAc (1:1 to 1:10 wt/wt) or IPA (1:1 to 1:10 wt/wt).

111. The process of any one of claims 106 to 110, wherein the step of distillation is performed at a temperature ranging from 30 °C to 90 °C.

112. The process of any one of claims 106 to 111, wherein the distillation is performed at NMT 75 °C.

113. The process of any one of claims 102 to 112, wherein the compound of Formula (II) is prepared by demethylating [4-[2-(dimethylamino)ethoxy]phenyl](4-hydroxyphenyl)methanone, a compound of Formula (I), wherein the compound of Formula (I) has the structure



with 1-chloroethyl chloroformate and DIPEA in THF to form the compound of Formula (II).

114. The process of claim 113, comprising the steps of:

(a) reacting the compound of Formula (I) with DIPEA in tetrahydrofuran;

(b) adding 1-chloroethyl chloroformate;

(c) distilling with methanol;

(d) reacting with methanol/6N HCl; and

(e) neutralizing with 8N NaOH.

115. The process of claim 113 or 114, comprising the steps of:

(a) reacting the compound of Formula (I) with DIPEA (1:1 to 1:10 wt/wt) in THF (1:20 wt/wt);

(b) adding 1-chloroethyl chloroformate (1:1 to 1:10 wt./wt);

(c) distilling with methanol one or more times (1:1 to 1:10 wt./wt);

(d) reacting with methanol (1:1 to 1:5 wt/wt)/6N HCl (1:1 to 1:10 wt/wt); and

(e) neutralizing with 8N NaOH (1:1 to 1:10 wt/wt);

wherein wt/wt is with respect to the compound of Formula (I).

116. The process of any one of claims 113 to 115, further comprising one or more steps of:

(a) washing the compound of Formula (II) with purified water (1:1 to 1:5 vol/wt);

(b) washing the compound of formula (II) with ethyl acetate (1:1 to 1: 5 wt/wt); and

(c) drying the compound of Formula (II) under reduced pressure at NMT 50°C;

wherein wt/wt is with respect to the compound of Formula (I).

117. The process of any one of claims 62 to 116, further comprising converting (E)-endoxifen to (Z)-endoxifen by reacting a mixture of (E)-endoxifen and (Z)-endoxifen to 6N HCl (1:1 to 1:5 wt/wt) in EtOAc (1:1 to 1:20 wt/wt), wherein wt/wt is with respect to the mixture of (E)-endoxifen and (Z)-endoxifen.

118. The process of claim 117, further comprising the steps of:

(a) neutralizing with 8N NaOH (1:1 to 1:20 wt/wt);

(b) extraction with ethyl acetate (1:1 to 1:10 wt/wt);

(c) one or more washes with 20% NaCl (1:1 to 1:10 wt/wt); and

(d) treatment with activated carbon (1:0.01 to 1:0.1 wt/wt);

wherein wt/wt is with respect to the compound of Formula (III).

119. A crystalline form of a compound of Formula (III) produced according to the method of any one of claims 62 to 118.

120. The crystalline form of claim 119, wherein the crystalline form is Form I of the compound of Formula (III).

121. An industrially scalable process of reequilibriating a mixture of (E)-endoxifen and (Z)-endoxifen having an E/Z ratio ranging from 45:55 to 55:45 comprising the steps of:

(a) reacting to 6N HCL (1:1 to 1:5 wt/wt) in ethyl acetate (1:1 to 1:20 wt/wt) a starting mixture of (E)-endoxifen and (Z)-endoxifen having an E/Z-ratio ranging from 99:1 to 60:40;

(b) neutralizing with 8N NaOH (1:1 to 1:20 wt/wt);

(c) washing one or more times with ethyl acetate; and

(d) washing one or more times with IPA;

wherein wt/wt is with respect the starting mixture of (E)-endoxifen and (Z)-endoxifen.

122. An industrially scalable process for manufacturing the crystalline form of any one of claims 12 to 31, comprising:

(a) reacting to 6N HCL (1:1 to 1:5 wt/wt) in ethyl acetate (1:1 to 1:20 wt/wt) a starting mixture of (E)-endoxifen and (Z)-endoxifen having an E/Z-ratio ranging from 99:1 to 40:60;

(b) neutralizing with 8N NaOH (1:1 to 1:20 wt/wt);

(c) washing one or more times with ethyl acetate;

(d) washing one or more times with a mixture of ethyl acetate and n-heptane; and

(e) recovering the crystalline form of any one of claims 12 to 31;

wherein wt/wt is with respect the starting mixture of (E)-endoxifen and (Z)-endoxifen.

123. A crystalline form of a compound of Formula (III) produced according to the method of claim 121 or 122.

124. The crystalline form of claim 123, wherein the crystalline form is Form II or Form III of the compound of Formula (III).

125. The process of any one of claims 62 to 122, wherein the (Z)-endoxifen is reacted with D-gluconate or L-Gluconate to form (Z)-endoxifen L-gluconate or (Z)-endoxifen D-gluconate.

126. The process of any one of claims 62 to 125, wherein the (Z)-endoxifen free base has < 1% impurity.

127. The process of any one of claims 62 to 126, wherein the (Z)-endoxifen free base is stable at ambient temperature for at least 9 months.

128. (Z)-endoxifen, (E)-endoxifen, a compound of Formula (III), a compound of Formula (II), or a salt thereof, prepared by the process of any one of claims 62 to 127.

129. A composition comprising (Z)-endoxifen free base or a salt thereof prepared by the process of any one of claims 62 to 127.

130. The composition of claim 129, wherein the composition is formulated for oral, parenteral, topical, or intraductal delivery.

131. The composition of claim 129 or 130, wherein the composition is formulated for oral delivery as a tablet, a caplet, a capsule, or a pill.

132. The composition of claim 131, having a mean half-life of endoxifen in a subject ranging from 30 hours to 60 hours after administration.

133. The composition of any one of claims 129 to 132, wherein the composition is formulated for oral delivery as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

134. The composition of any one of claims 129 to 133, wherein the composition is administered to a subject for the treatment or prevention of a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both in the subject.

135. An oral composition comprising 1 mg to 200 mg per unit dose of (Z)-endoxifen free base or a salt thereof, for administration to a subject in need thereof, wherein daily administration of the oral composition achieves in the subject:

(a) a steady state plasma level of endoxifen within 7 to 21 days;

(b) a steady state plasma level of endoxifen ranging from 25 nM to 300 nM;

(c) a steady state plasma level of endoxifen greater than 30 nM;

(d) maximal plasma levels of endoxifen within 2 to 10 hours after administering; or

(e) any combination thereof.

136. The oral composition of claim 135, having a mean half-life of endoxifen in a subject ranging from 40 hours to 55 hours after administration.

137. The oral composition of claim 135 or 136, wherein the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

138. The oral composition of claim 133 or 137, wherein at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% endoxifen is released in the intestines.

139. The composition or oral composition of any one of claims 129 to 138, having a mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) of 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL.

140. A method of treating a subject in need thereof, the method comprising administering to the subject an oral composition of any one of claims 129 to 139.

141. The method of claim 140, wherein the subject has or is at risk of having a hormone-dependent breast disorder, a hormone-dependent reproductive tract disorder, or both.

142. The method of claim 141, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

143. The method of claim 141 or 142, wherein the subject has prostate cancer and wherein the subject further has or is at risk of having gynecomastia.

144. The method of any one of claims 141 to 143, wherein the subject has tamoxifen-refractory or tamoxifen resistant hormone-dependent breast disorder or hormone-dependent reproductive tract disorder.

145. The method of any one of claims 141 to 144, wherein the subject is or will be treated with an SSRI drug selected from the group consisting of citalopram, escitalopram, fluoxetine, paroxetine, sertraline, and vilazodone.

146. The method of any one of claims 141 to 145, wherein the subject is administered 0.01 mg to 200 mg of (Z)-endoxifen.

147. The method of any one of claims 141 to 146, wherein the subject is administered 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen daily.

148. The method of any one of claims 141 to 147, wherein a steady state plasma level of endoxifen in the subject is greater than 30 nM.

149. The method of any one of claims 141 to 148, wherein the steady state plasma level of endoxifen is achieved within 7 to 21 days of the first administration of the composition.

150. The method of any one of claims 141 to 149, wherein time to maximum plasma levels of endoxifen ranges from 2 hours to 10 hours or from 4 hours to 8 hours after administering the composition.

151. A method of treating a subject having or at risk of having a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder or both, the method comprising administering an oral composition comprising (Z)-endoxifen or a salt thereof, wherein administration of the composition achieves:

(a) a mean half-life of endoxifen in the subject ranging from 30 hours to 60 hours after administration;

(b) a time to maximum plasma levels of endoxifen ranging from 4 hours to 8 hours after administration; and

(c) a steady state plasma level of endoxifen greater than 30 nM.

152. The method of claim 151, wherein the subject is administered 1 mg, 2 mg, 4 mg, 6 mg, 10 mg or 20 mg of (Z)-endoxifen.

153. The method of claim 151 or 152, wherein the mean area under the curve extrapolated to time infinity ($AUC_{0\text{-}inf}$) is 200 hr*ng/mL to 10000 hr*ng/mL, of 300 hr*ng/mL to 8000 hr*ng/mL, of 400 hr*ng/mL to 6000 hr*ng/mL or of 700 hr*ng/mL to 6000 hr*ng/mL.

154. The method of any one of claims 151 to 153, wherein the composition is formulated as an enteric tablet, an enteric caplet, an enteric capsule, a delayed-release tablet, a delayed-release caplet or a delayed-release capsule.

155. The method of any one of claims 151 to 154, wherein at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90% of the endoxifen is released in the intestines.

156. The method of claim 151 or 155, wherein the composition is administered once a day, twice a day, thrice a day, four times a day, every other day, twice a week, weekly, fortnightly, twice a month, monthly, quarterly, once every six months, or annually.

157. The method of any one of claims 151 to 156, wherein the hormone-dependent breast disorder and the hormone-dependent reproductive tract disorder are selected from the group consisting of benign breast disorders, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, DCIS, LCIS, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, and vulvar cancer.

ABSTRACT OF THE DISCLOSURE

The present disclosure provides industrially scalable methods of making (Z)-endoxifen or a salt thereof, crystalline forms of endoxifin, and compositions comprising them. The present disclosure also provides methods for treating hormone-dependent breast and hormone-dependent reproductive tract disorders.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Steven	C.	Quay	

Residence Information (Select One) ● US Residency ○ Non US Residency ○ Active US Military Service

City	State/Province	Country of Residence
Seattle	WA	US

Mailing Address of Inventor:

Address 1	107 Spring Street
Address 2	

City	State/Province	Postal Code	Country
Seattle	WA	98104	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Yao-Lin		Sun	

Residence Information (Select One) ○ US Residency ● Non US Residency ○ Active US Military Service

City	Country of Residence
Tainan City	TW

Mailing Address of Inventor:

Address 1	107 Spring Street
Address 2	

City	State/Province	Postal Code	Country
Seattle	WA	98104	US

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	LungHu		Wang	

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Residence Information (Select One) ○ US Residency ◉ Non US Residency Active US Military Service

City	Kaohsiung City	Country of Residence [i]	TW

Mailing Address of Inventor:

Address 1	107 Spring Street		
Address 2			
City	Seattle	State/Province	WA
Postal Code	98104	Country [i]	US

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	ChangJung		Wu	

Residence Information (Select One) ○ US Residency ◉ Non US Residency Active US Military Service

City	Kaohsiung City	Country of Residence [i]	TW

Mailing Address of Inventor:

Address 1	107 Spring Street		
Address 2			
City	Seattle	State/Province	WA
Postal Code	98104	Country [i]	US

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	ChuanDer		Huang	

Residence Information (Select One) ○ US Residency ◉ Non US Residency Active US Military Service

City	Tainan City	Country of Residence [i]	TW

Mailing Address of Inventor:

Address 1	107 Spring Street		
Address 2			
City	Seattle	State/Province	WA
Postal Code	98104	Country [i]	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
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Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below. For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	187495		
Email Address	seattlepatentdocket@us.dlapiper.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS FOR MAKING AND USING ENDOXIFEN		
Attorney Docket Number	438558-758053	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	13	**Suggested Figure for Publication (if any)**	3

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

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Customer Number	187495		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	18090757	2022-12-29
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
18090757	Continuation of	17580428	2022-01-20	11572334	2023-02-07

Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17580428	Continuation of	16641985	2020-02-25	11261151	2022-03-01

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
16641985	a 371 of international	PCT/US18/50272	2018-09-10
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US18/50272	Claims benefit of provisional	62693885	2018-07-03
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US18/50272	Claims benefit of provisional	62624787	2018-01-31
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US18/50272	Claims benefit of provisional	62556799	2017-09-11

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US18/50272	Claims benefit of provisional	62556884	2017-09-11
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Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

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Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.			Add

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

● Assignee	Legal Representative under 35 U.S.C. 117	Joint Inventor
Person to whom the inventor is obligated to assign.	Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name: Atossa Therapeutics, Inc.

Mailing Address Information For Applicant:

Address 1	107 Spring Street		
Address 2			
City	Seattle	**State/Province**	WA
Country	US	Postal Code	98104
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button. Add

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

Remove

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country i		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

Signature:

Remove

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Erin M. Gaffney/			Date (YYYY-MM-DD)	2023-03-30
First Name	Erin M.	Last Name	Gaffney, Ph.D.	Registration Number	81,479

Additional Signature may be generated within this form by selecting the Add button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

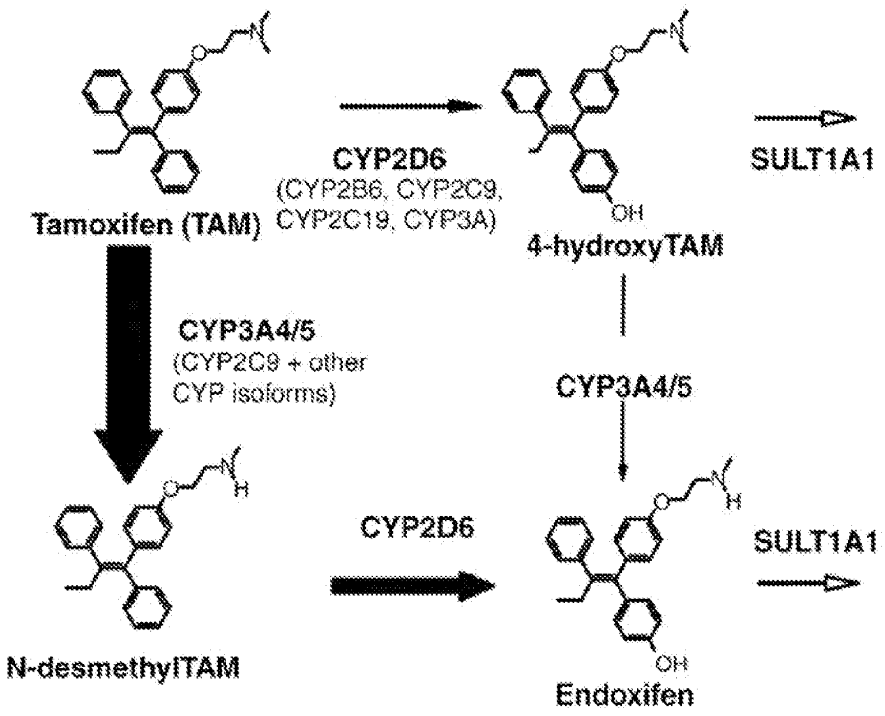
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Fig. 1



PRIOR ART

Fig. 2

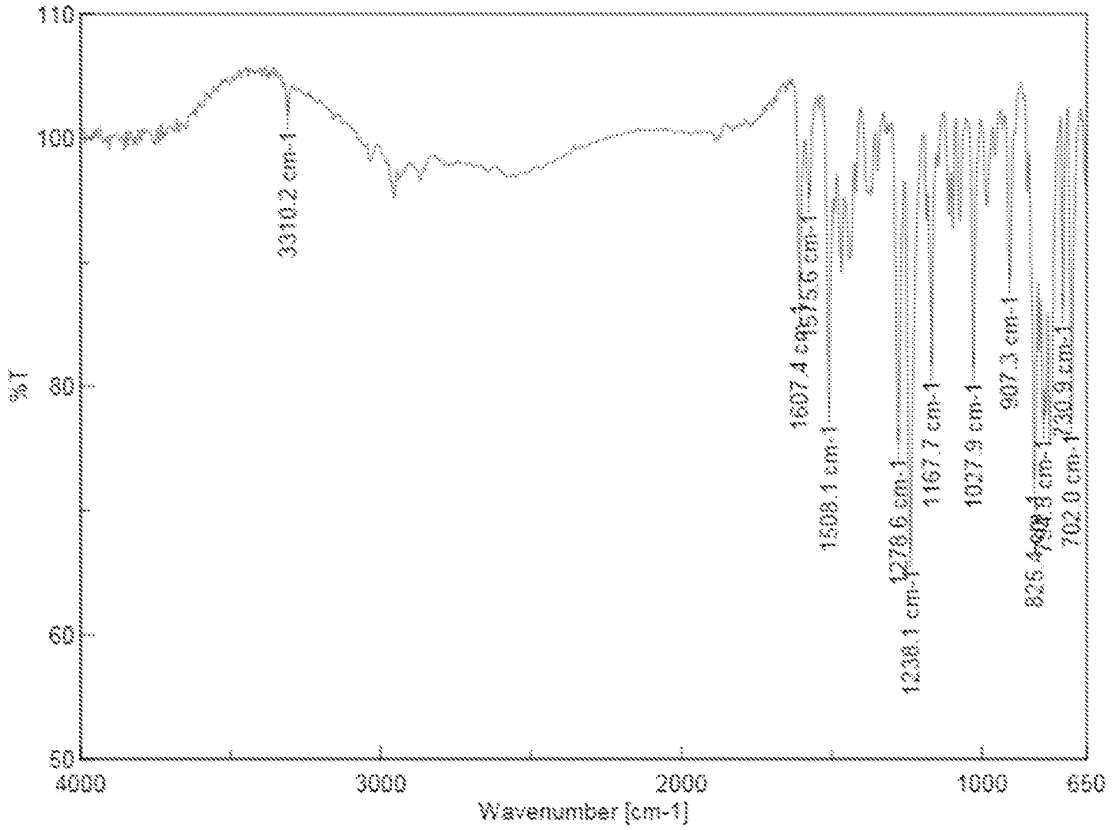

110
100
90
80
50
%T
4000
3000
2000
1000
650
Wavenumber [cm-1]
3310.2 cm-1
1607.4 cm-1
1576 cm-1
1508.1 cm-1
1238.1 cm-1
1270.6 cm-1
1167.7 cm-1
1027.9 cm-1
907.3 cm-1
825.4 cm-1
730.9 cm-1
702.0 cm-1

Fig. 3

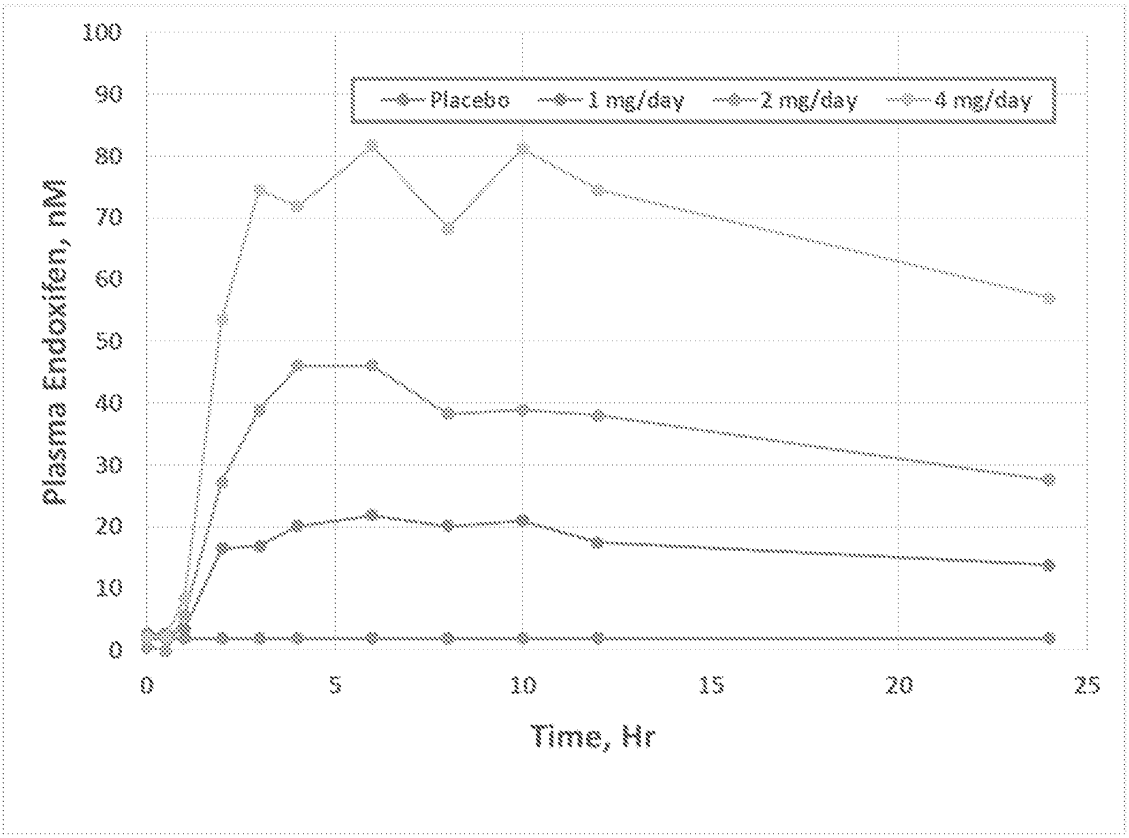

Placebo
1 mg/day
2 mg/day
4 mg/day
Plasma Endoxifen, nM
Time, Hr
0
10
20
30
40
50
60
70
80
90
100
0
5
10
15
20
25

Fig. 4

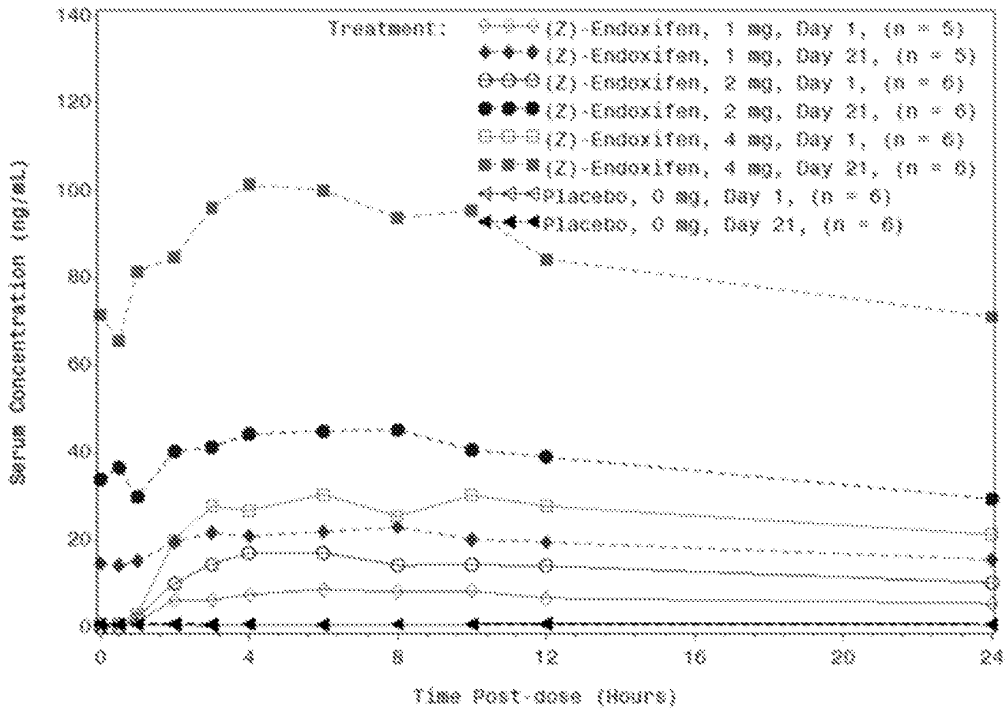

Treatment:
(Z)-Endoxifen, 1 mg, Day 1, (n = 5)
(Z)-Endoxifen, 1 mg, Day 21, (n = 5)
(Z)-Endoxifen, 2 mg, Day 1, (n = 6)
(Z)-Endoxifen, 2 mg, Day 21, (n = 6)
(Z)-Endoxifen, 4 mg, Day 1, (n = 6)
(Z)-Endoxifen, 4 mg, Day 21, (n = 6)
Placebo, 0 mg, Day 1, (n = 6)
Placebo, 0 mg, Day 21, (n = 6)
Serum Concentration (ng/mL)
0
20
40
60
80
100
120
140
0
4
8
12
16
20
24
Time Post-dose (Hours)

Fig. 5

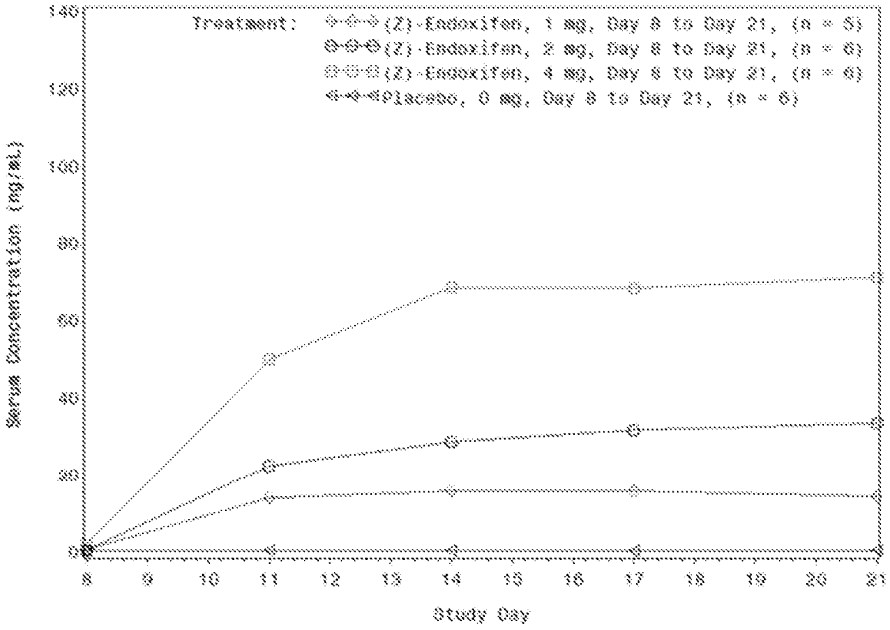

Treatment:
(Z)-Endoxifen, 1 mg, Day 8 to Day 21, (n = 5)
(Z)-Endoxifen, 2 mg, Day 8 to Day 21, (n = 6)
(Z)-Endoxifen, 4 mg, Day 8 to Day 21, (n = 6)
Placebo, 0 mg, Day 8 to Day 21, (n = 6)
Serum Concentration (ng/mL)
0
20
40
60
80
100
120
140
8
9
10
11
12
13
14
15
16
17
18
19
20
21
Study Day

Fig. 6

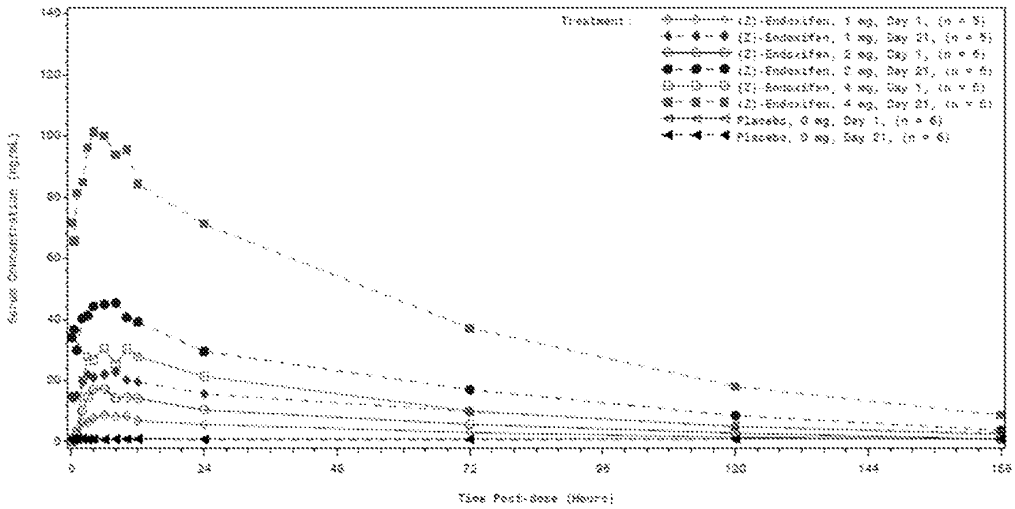

Treatment:
(Z)-Endoxifen, 1 mg, Day 1, (n = 5)
(Z)-Endoxifen, 1 mg, Day 21, (n = 5)
(Z)-Endoxifen, 2 mg, Day 1, (n = 6)
(Z)-Endoxifen, 2 mg, Day 21, (n = 5)
(Z)-Endoxifen, 4 mg, Day 1, (n = 5)
(Z)-Endoxifen, 4 mg, Day 21, (n = 5)
Placebo, 0 mg, Day 1, (n = 6)
Placebo, 0 mg, Day 21, (n = 6)
Serum Concentration (ng/mL)
0
20
40
60
80
100
120
140
0
24
48
72
96
120
144
168
Time Post-Dose (Hours)

Fig. 7

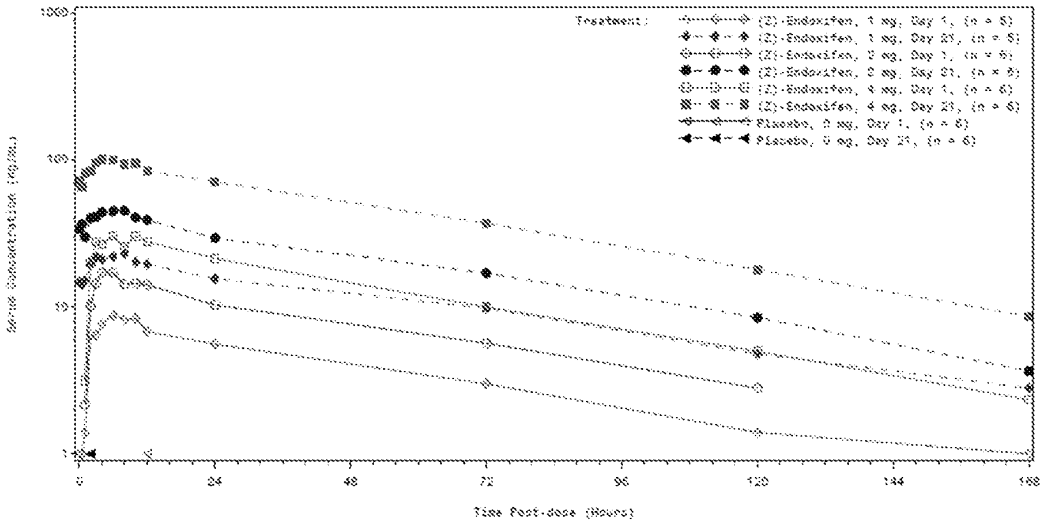
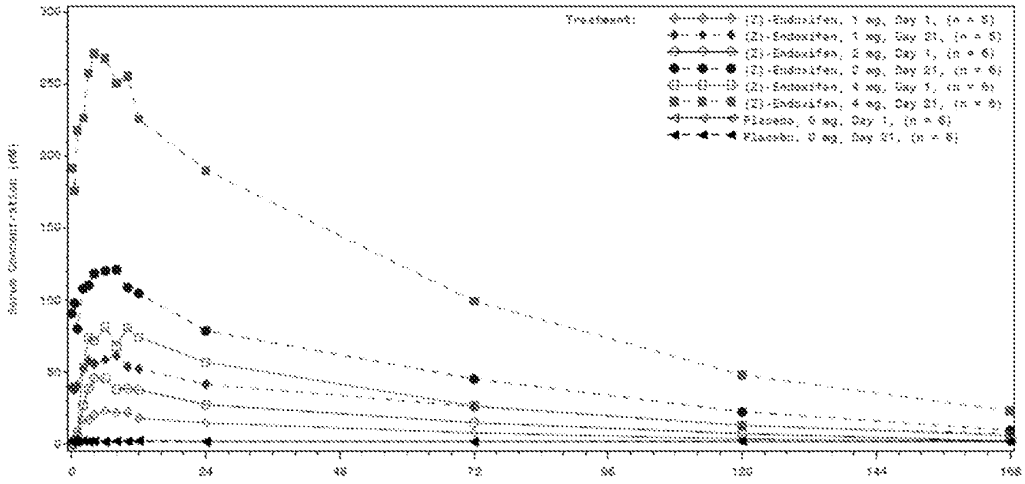

Treatment:
(Z)-Endoxifen, 1 mg, Day 1, (n = 5)
(Z)-Endoxifen, 1 mg, Day 21, (n = 5)
(Z)-Endoxifen, 2 mg, Day 1, (n = 6)
(Z)-Endoxifen, 2 mg, Day 21, (n = 6)
(Z)-Endoxifen, 4 mg, Day 1, (n = 6)
(Z)-Endoxifen, 4 mg, Day 21, (n = 6)
Placebo, 2 mg, Day 1, (n = 6)
Placebo, 4 mg, Day 21, (n = 6)
Serum Concentration (ng/mL)
1000
100
10
1
0
24
48
72
96
120
144
168
Time Post-dose (Hours)

Fig. 8


Treatment:
(Z)-Endoxifen, 1 mg, Day 1, (n = 5)
(Z)-Endoxifen, 1 mg, Day 21, (n = 5)
(Z)-Endoxifen, 2 mg, Day 1, (n = 6)
(Z)-Endoxifen, 2 mg, Day 21, (n = 6)
(Z)-Endoxifen, 4 mg, Day 1, (n = 6)
(Z)-Endoxifen, 4 mg, Day 21, (n = 6)
Placebo, 0 mg, Day 1, (n = 6)
Placebo, 0 mg, Day 21, (n = 6)
Serum Concentration (nM)
300
250
200
150
100
50
0
0
24
48
72
96
120
144
168

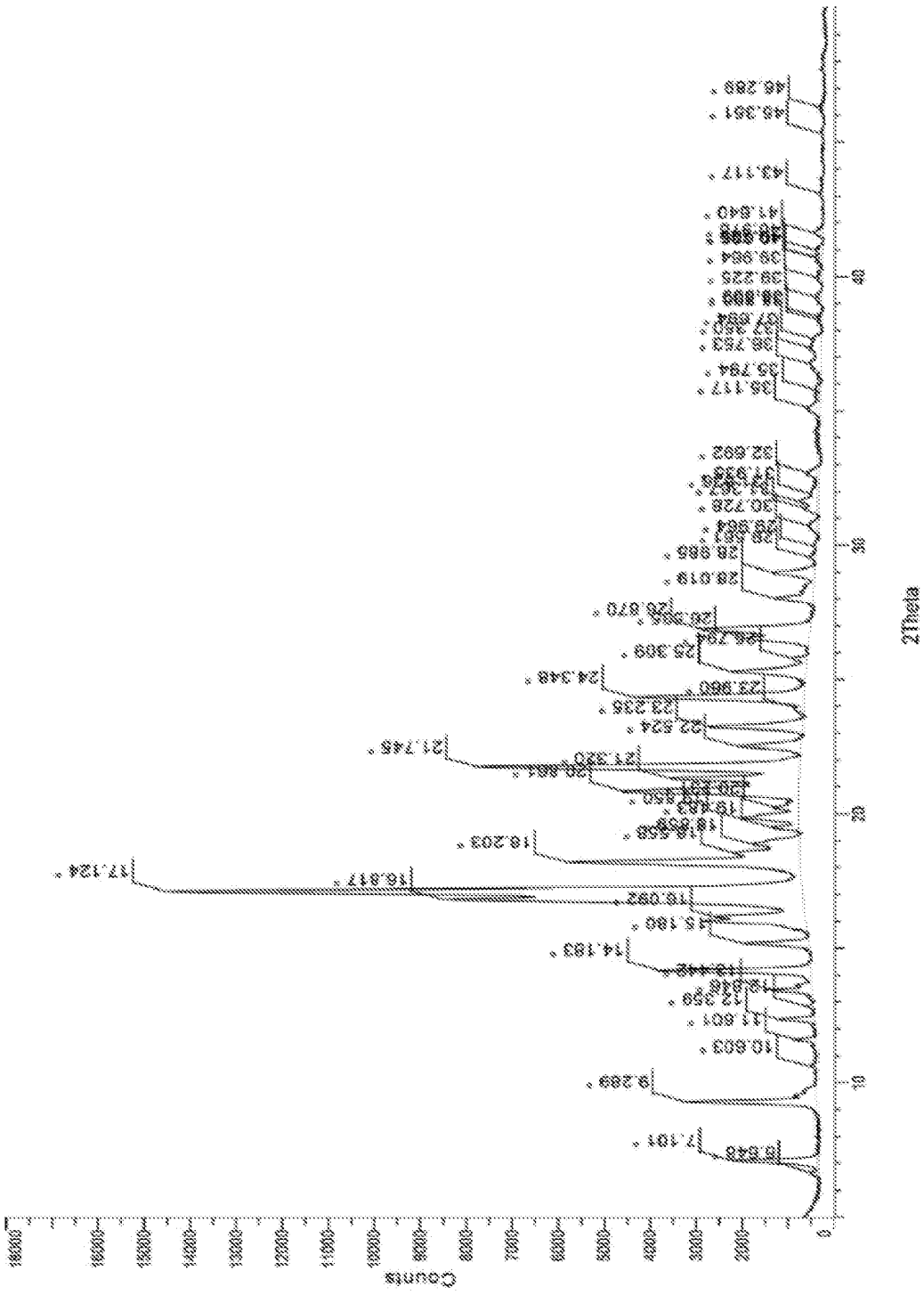

Counts
2Theta
7.101
9.299
10.603
11.601
12.299
14.183
16.817
17.124
18.203
21.745
24.348
25.309
28.019
30.728
32.602
35.794
43.117
46.361

Fig. 9

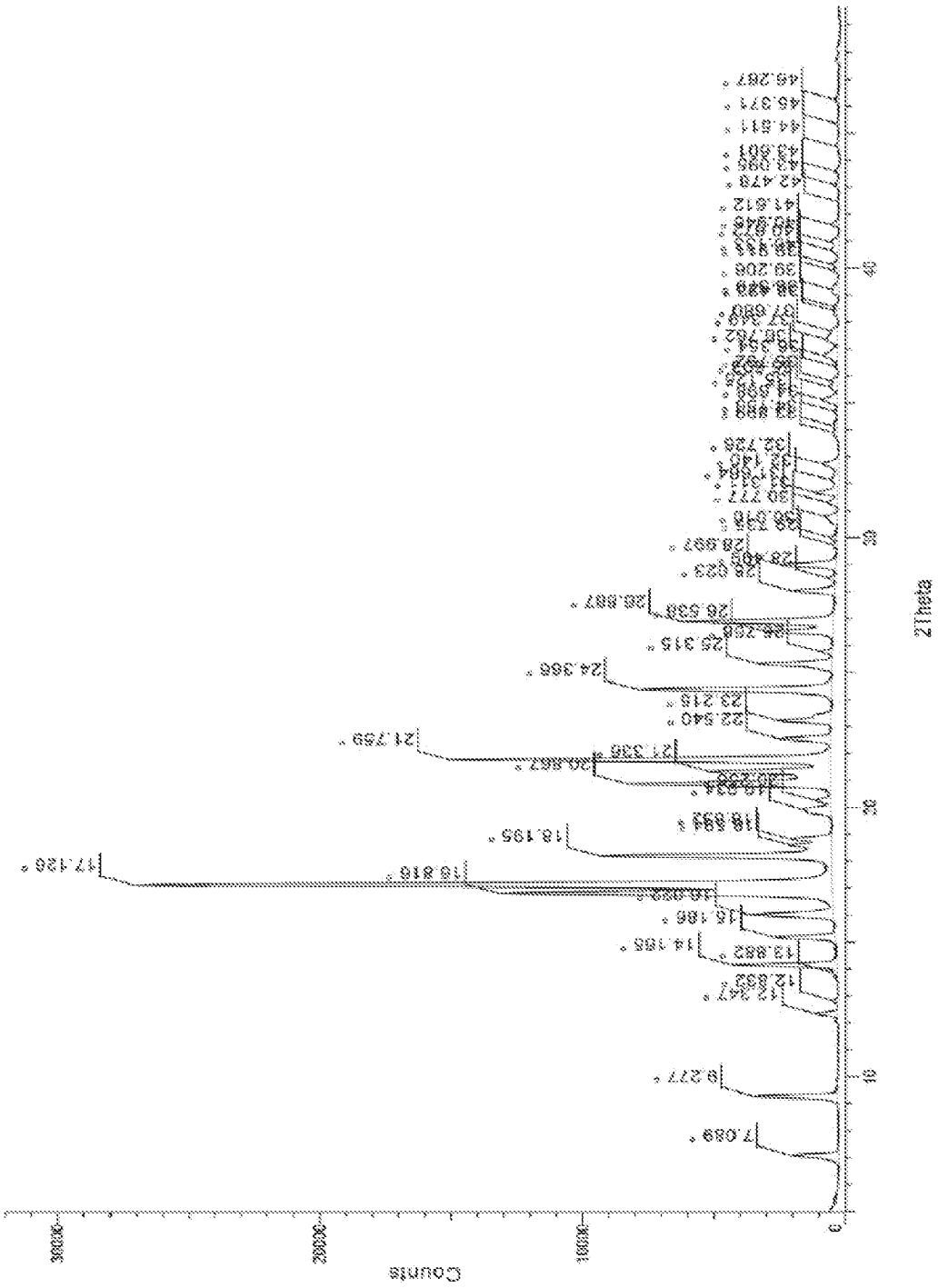

Counts
2Theta
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9.277
12.347
12.895
13.852
14.185
16.186
17.126
18.816
18.994
19.195
21.759
22.540
23.218
24.366
25.315
26.807
28.023
28.897
46.287
46.371
44.811
43.601
43.095
42.478

Fig. 10

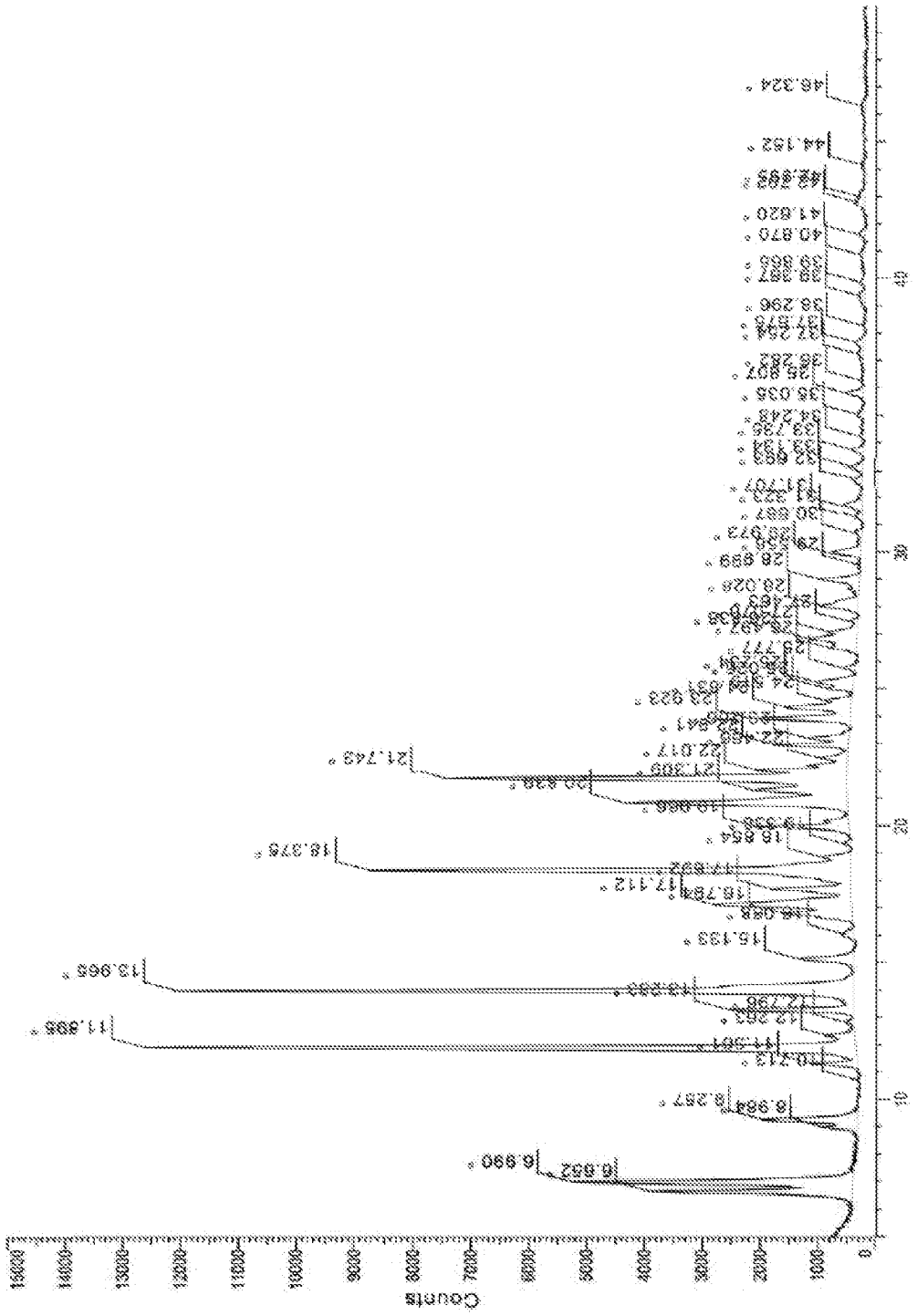

Counts
2Theta
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6.990
8.267
10.213
11.301
11.898
12.392
13.965
15.133
16.654
16.778
17.112
18.379
21.743
46.324

Fig. 11

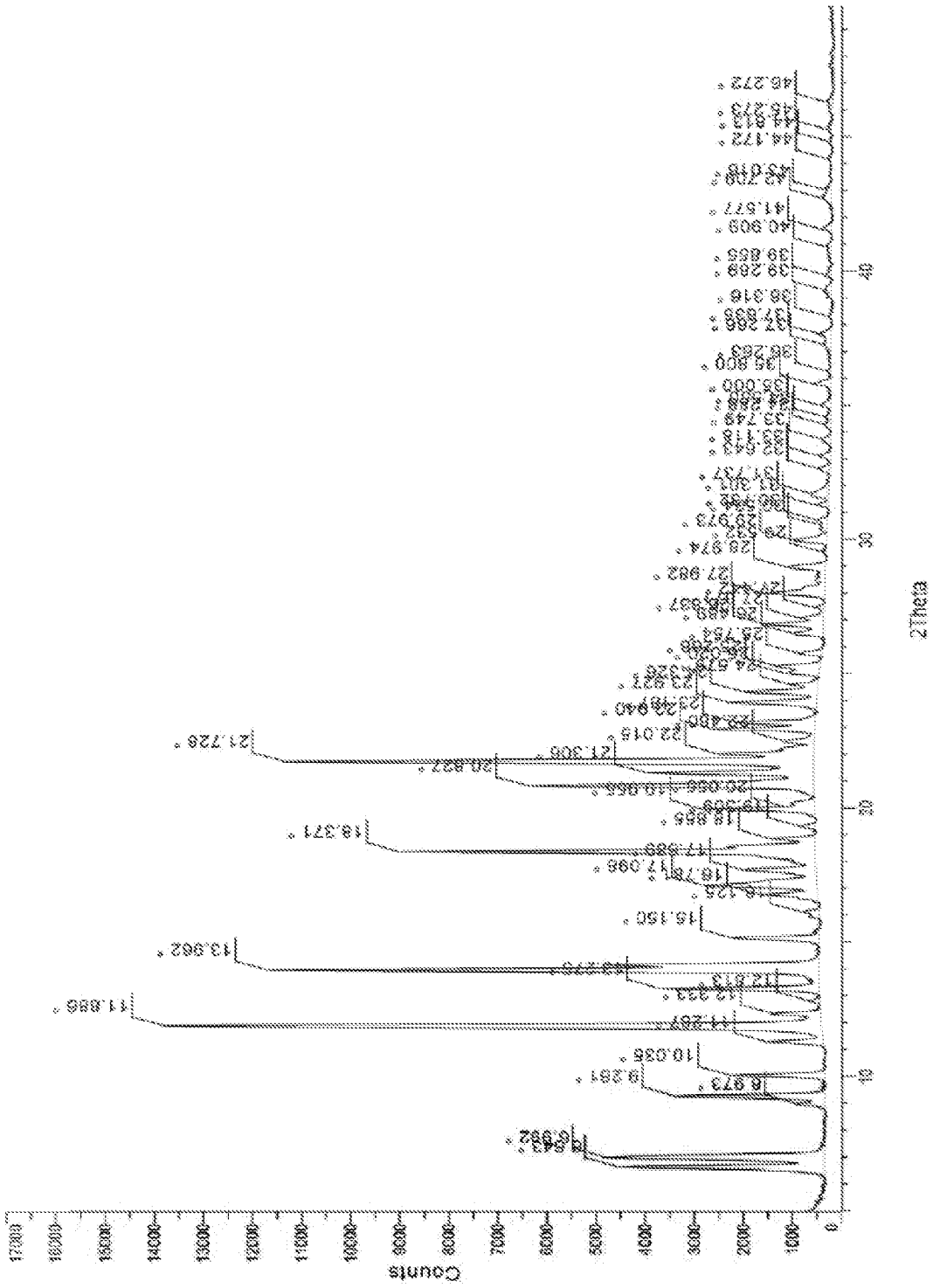

Counts
2Theta
6.382°
8.973°
9.261°
10.036°
11.287°
11.886°
13.962°
15.150°
18.371°
21.726°

Fig. 12

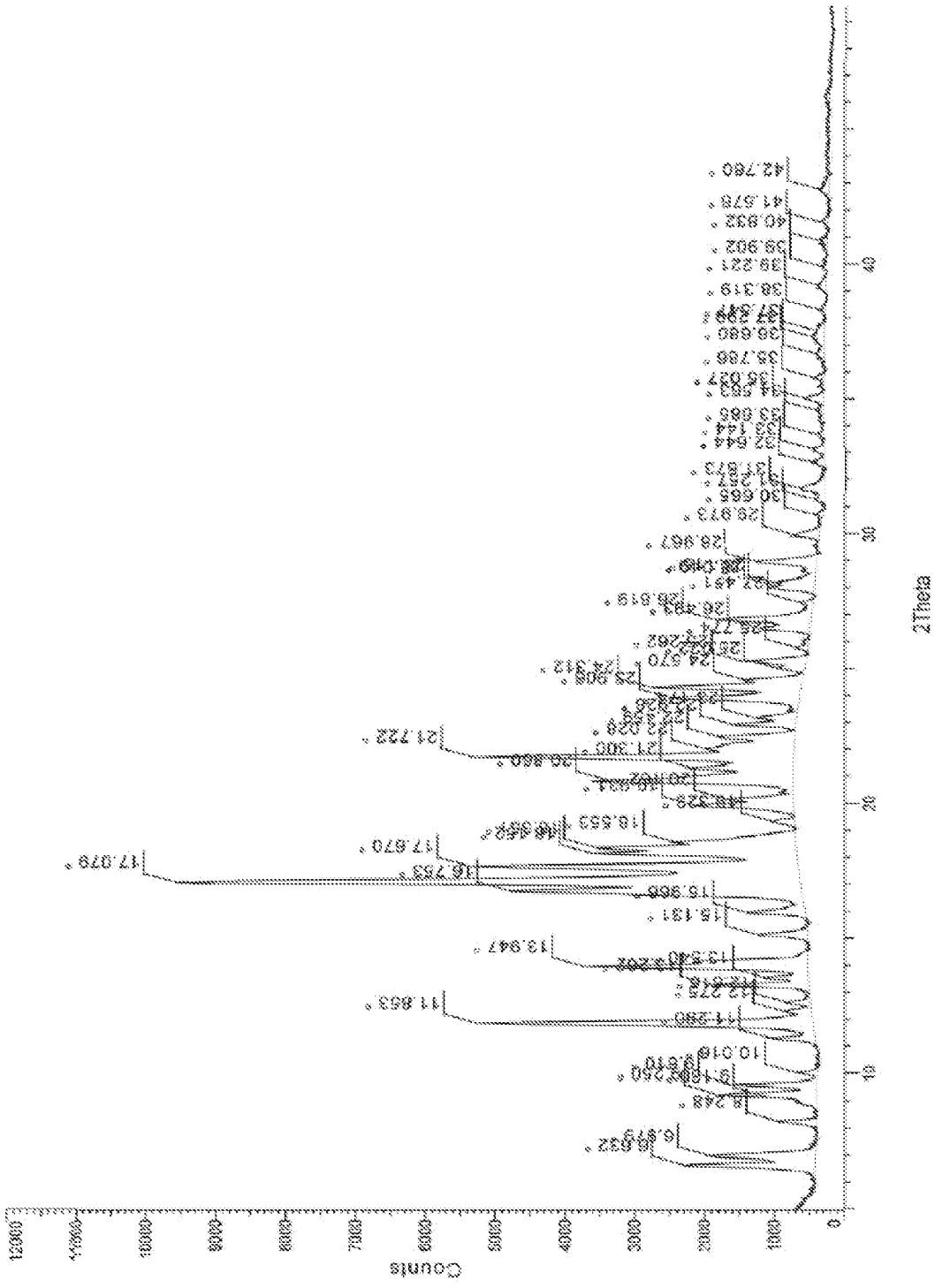

Counts
2Theta
6.879
8.248
10.018
11.863
13.947
15.131
16.763
17.079
17.670
18.653
21.722
42.760

Fig. 13

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number PCT/US2018/050272

filed on September 10, 2018

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Steven C. Quay Date (Optional): 09/27/2018

Signature:

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number 17/580,428 filed on January 20, 2022.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: Yao-Lin Sun Date (Optional): 2022/09/19

Signature: Yao-Lin Sun

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Attorney Docket No.: 38602-758.831

PTO/AIA/01 (06-12)
Approved for use through 11/30/2020. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN

As the below named inventor, I hereby declare that:

This declaration is directed to:

☐ The attached application, or

☒ United States application or PCT international application number PCT/US2018/050272 filed on September 10, 2018.

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: LungHu Wang Date (Optional): 2018/09/19

Signature: LungHu Wang

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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LEGAL NAME OF INVENTOR

Inventor: ChangJung Wu Date (Optional): 2018/09/19.

Signature: ChangJung Wu.

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

This collection of information is required by 35 U.S.C. 115 and 37 CFR 1.63. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 1 minute to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Attorney Docket No.: 38602-758.831

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The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

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WARNING:

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LEGAL NAME OF INVENTOR

Inventor: ChuanDer Huang Date (Optional): 2018/09/26

Signature: C.D. Huang

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
18/128,536	03/30/2023		0	438558-758053	157	8

CONFIRMATION NO. 1025

FILING RECEIPT

187495
DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

Date Mailed: 05/04/2023

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Steven C. Quay, Seattle, WA;
Yao-Lin Sun, Tainan City, TAIWAN;
LungHu Wang, Kaohsiung City, TAIWAN;
ChangJung Wu, Kaohsiung City, TAIWAN;
ChuanDer Huang, Tainan City, TAIWAN;

Applicant(s)

Atossa Therapeutics, Inc., Seattle, WA;

Power of Attorney: The patent practitioners associated with Customer Number 187495

Domestic Priority data as claimed by applicant

This application is a CON of 18/090,757 12/29/2022
which is a CON of 17/580,428 01/20/2022 PAT 11,572,334
which is a CON of 16/641,985 02/25/2020 PAT 11,261,151
which is a 371 of PCT/US18/50272 09/10/2018
which claims benefit of 62/693,885 07/03/2018
and claims benefit of 62/624,787 01/31/2018
and claims benefit of 62/556,799 09/11/2017
and claims benefit of 62/556,884 09/11/2017

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 05/02/2023

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/128,536**

Projected Publication Date: To Be Determined - pending completion of Missing Parts.

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

METHODS FOR MAKING AND USING ENDOXIFEN

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign

patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET Substitute for Form PTO-1360 (For use with Form PTO/SB/06)	Application Number 18/128,536	Filing Date
	Applicant(s) Steven C. Quay	

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1					
2		1				
3		1				
4		1				
5		1				
6		2				
7		1				
8		(1)				
9		(1)				
10		(1)				
11		(1)				
12		1				
13		1				
14		2				
15		2				
16		2				
17		(1)				
18		2				
19		(1)				
20		(1)				
21		(1)				
22		(1)				
23		2				
24		2				
25		2				
26		(1)				
27		2				
28		(1)				
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31		(1)				
32	1					
33		(1)				
34		(1)				
35		(1)				
36		(1)				
37		(1)				
38	1					
39		1				
40		2				
41		(1)				
42		(1)				
43		(1)				
44		(1)				
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	Indep	Depend	Indep	Depend	Indep	Depend
51		(1)				
52		(1)				
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57		(1)				
58		(1)				
59		(1)				
60		(1)				
61		(1)				
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97		(1)				
98		(1)				
99		(1)				
100	1					

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET Substitute for Form PTO-1360 (For use with Form PTO/SB/06)	Application Number 18/128,536	Filing Date
	Applicant(s) Steven C. Quay	

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
101		(1)				
102		(1)				
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135	1					
136		1				
137		2				
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Total Indep	8					
Total Depend	161	↵		↵		↵
Total Claims			0		0	

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	Indep	Depend	Indep	Depend	Indep	Depend
151	1					
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153		2				
154		(1)				
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 18/128,536

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	64		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	280		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	320		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	169 minus 20 =	* 149	x 40 =	5960	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	8 minus 3 =	* 5	x 192 =	960			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			168			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				344			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	2136		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/128,536	03/30/2023	Steven C. Quay	438558-758053

CONFIRMATION NO. 1025

187495
DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

FORMALITIES LETTER

OC000000056656561

Date Mailed: 05/04/2023

NOTICE TO FILE MISSING PARTS OF NONPROVISIONAL APPLICATION

FILED UNDER 37 CFR 1.53(b)

Filing Date Granted

An application number and filing date have been accorded to the above-identified nonprovisional application. The item(s) indicated below, however, are missing. Applicant is given **TWO MONTHS** from the date of this Notice within which to file all required items below to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

- The statutory basic filing fee has not been received.
- The application search fee must be submitted.
- The application examination fee must be submitted.
- Additional claim fees of $**7264** as a small entity, including any required multiple dependent claim fee, are required. Applicant must submit the additional claim fees or cancel the additional claims for which fees are due.
- Surcharge as set forth in 37 CFR 1.16(f) has not been received.

  The surcharge is due for any one of:
  - late submission of the basic filing fee, search fee, or examination fee,
  - late submission of inventor's oath or declaration,
  - filing an application that does not contain at least one claim on filing, or
  - submission of an application filed by reference to a previously filed application.

SUMMARY OF FEES DUE:

The fee(s) required (including the fees noted above) are as follows. Small entity discount is in effect. If applicant is qualified for micro entity status, an acceptable Certification of Micro Entity Status must be submitted to establish micro entity status. (See 37 CFR 1.29 and forms PTO/SB/15A and 15B.)

- $**64** basic filing fee.
- $**168** for **11** pages in excess of **100** application size fee.
- $**64** surcharge.
- $**280** search fee.
- $**320** examination fee.
- $**960** for 5 independent claims over 3.

- $**5960** for 149 total claims over 20.
- $**344** for multiple dependent claim surcharge.
- $(**0**) previous unapplied payment amount.
- $**8160** TOTAL FEE BALANCE DUE.

Replies must be received in the USPTO within the set time period or must include a proper Certificate of Mailing or Transmission under 37 CFR 1.8 with a mailing or transmission date within the set time period. For more information and a suggested format, see Form PTO/SB/92 and MPEP 512.

Replies should be addressed to:

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

REPLY VIA ELECTRONIC FILING

A reply may be submitted via electronic filing only by registered users of the appropriate USPTO patent electronic filing system and must include:

- A separate document having the document description, "**Applicant response to Pre-Exam Formalities Notice**"; and
- the item(s) for which a reply period is set forth above.

For more information about electronic filing, contact the Patent Electronic Business Center (EBC) 1-866-217-9197 or visit https://www.uspto.gov/ebc

NOTE: If the reply is not being submitted electronically, a copy of this notice must be included.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/eruga/

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on August 4, 2023

DLA PIPER LLP (US)

By: /Christina Campbell/

Attorney Docket No.: 438558-758053

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Confirmation No.: 1025
Steven C. Quay et al.	
Application No.: 18/128,536	Examiner: Unassigned
Filed: March 30, 2023	Art Unit: Unassigned
For: METHODS FOR MAKING AND USING ENDOXIFEN	PRELIMINARY AMENDMENT
Customer No.: 187495	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Prior to examination on the merits of the above-referenced application, please enter the following amendments and remarks:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 7 of this paper.

Intas Exhibit 1002
Page 180 of 408
PGR2025-00043

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

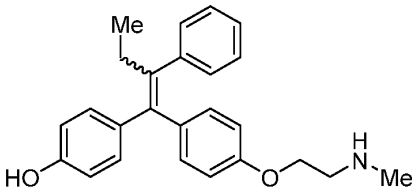
Listing of Claims:

1-157. (Canceled)

158. (New) A composition comprising an endoxifen and an enteric material,

wherein:

the endoxifen comprises a compound of Formula (III):



Formula (III)

or a pharmaceutically acceptable salt thereof; and

at least 90% by weight of the compound of Formula (III) is (*Z*)-endoxifen.

159. (New) The composition of claim 158, wherein the pharmaceutically acceptable salt is selected from the group consisting of an: arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, Teoclate, triethiodide, benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc salt.

160. (New) The composition of claim 158, wherein the pharmaceutically acceptable salt of the compound of Formula (III) is endoxifen gluconate.

161. (New) The composition of claim 158, wherein the composition is a delayed-release formulation.

162. (New) The composition of claim 158, wherein the composition is a tablet.

163. (New) The composition of claim 158, wherein the composition is a capsule.

164. (New) The composition of claim 158, wherein the composition is uncoated.

165. (New) The composition of claim 158, wherein the composition comprises an enteric coating.

166. (New) The composition of claim 158, wherein the composition is formulated as a suspension.

167. (New) The composition of claim 166, wherein the suspension comprises a syrup or an elixir.

168. (New) The composition of claim 166, wherein the suspension comprises a fluid.

169. (New) The composition of claim 168, wherein the fluid comprises an alcohol.

170. (New) The composition of claim 169, wherein the alcohol comprises ethanol.

171. (New) The composition of claim 166, wherein the suspension comprises an alcohol, a plant oil, a mineral oil, a glycol, an agar, or a mixture thereof.

172. (New) The composition of claim 166, wherein the suspension comprises ethanol, mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, vegetable oil, stearic acid, sodium lauryl sulfate, or a mixture thereof.

173. (New) The composition of claim 158, wherein the compound of Formula (III) is stable in the composition for at least 10 days at about 25°C.

174. (New) The composition of claim 158, formulated such that the composition is resistant to dissolution in an acidic environment for at least 2 hours, as measured in a dissolution test performed according to a method of USP 711.

175. (New) The composition of claim 158, formulated such that the composition releases no more than 10% of the (*Z*)-endoxifen over 2 hours in gastric fluid, as measured in a dissolution test performed according to a method of USP 711.

176. (New) The composition of claim 158, formulated such that the composition releases at least 50% of the (*Z*)-endoxifen within 8 hours in intestinal fluid, as measured in a dissolution test performed according to a method of USP 711.

177. (New) The composition of claim 158, wherein the composition further comprises hydroxypropylmethyl cellulose.

178. (New) The composition of claim 158, wherein the composition further comprises a filler.

179. (New) The composition of claim 178, wherein the filler comprises a sugar, salt, talc, calcium carbonate, microcrystalline cellulose, methyl cellulose, carboxymethyl cellulose, kaolin, mannitol, silicic acid, sorbitol, starch, pregelatinized starch, or combinations thereof.

180. (New) The composition of claim 158, wherein the composition further comprises a disintegrant.

181. (New) The composition of claim 158, wherein the composition further comprises a lubricant.

182. (New) The composition of claim 181, wherein the lubricant comprises calcium stearate, magnesium stearate, zinc stearate, mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil, ethyl oleate, ethyl laureate, agar, or combinations thereof.

183. (New) The composition of claim 158, wherein the composition comprises from 0.01 mg to 200 mg (*Z*)-endoxifen.

184. (New) The composition of claim 158, wherein the composition comprises from 1 mg to 20 mg of (*Z*)-endoxifen.

185. (New) The composition of claim 158, wherein the composition comprises from 1 mg to 4 mg of (*Z*)-endoxifen.

186. (New) The composition of claim 158, wherein the composition comprises 8 mg of (*Z*)-endoxifen.

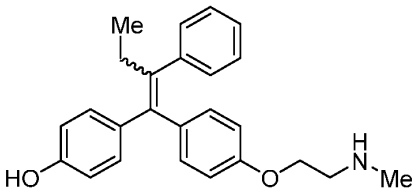
187. (New) A method of making the composition of claim 166, the method comprising suspending the endoxifen and the enteric material in a fluid.

188. (New) The method of claim 187, wherein the fluid comprises an alcohol, ethanol, a plant oil, a mineral oil, a glycol, an agar, glycerin, sorbitol, mannitol, polyethylene glycol, vegetable oil, stearic acid, sodium lauryl sulfate, or a mixture thereof.

189. (New) A method comprising administering to a subject a composition comprising an endoxifen and an enteric material,

wherein:

the endoxifen comprises a compound of Formula (III):



Formula (III)

or a pharmaceutically acceptable salt thereof; and

at least 90% by weight of the compound of Formula (III) is (*Z*)-endoxifen.

190. (New) The method of claim 189, comprising administering 1 mg to 20 mg of (*Z*)-endoxifen.

191. (New) The method of claim 189, comprising administering 1 mg to 4 mg of (*Z*)-endoxifen.

192. (New) The method of claim 189, comprising administering 8 mg of (*Z*)-endoxifen.

193. (New) The method of claim 189, wherein the administering of the composition maintains the subject's plasma endoxifen at a steady state level above 30 nM.

194. (New) The method of claim 189, wherein the administering of the composition maintains the subject's plasma endoxifen at a steady state level from 30 nM to 300 nM.

195. (New) The method of claim 189, further comprising releasing no more than 10% of the (*Z*)-endoxifen in a stomach of the subject within 2 hours following the administrating of the composition.

196. (New) The method of claim 189, further comprising releasing at least 50% of the (*Z*)-endoxifen in a small intestine of the subject within 8 hours following the administrating of the composition.

197. (New) The method of claim 189, further comprising producing an area under curve ($AUC_{0\text{-}inf}$) of (*Z*)-endoxifen in the subject of from 200 hr*ng/mL to 10,000 hr*ng/mL per 4 mg of (*Z*)-endoxifen administered.

198. (New) The method of claim 189, further comprising producing a maximum blood plasma concentration (C_{max}) of (*Z*)-endoxifen in the subject of from 14 ng/mL to 62 ng/mL per 4 mg of (*Z*)-endoxifen administered.

199. (New) The method of claim 189, further comprising treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in the subject in need thereof.

200. (New) The method of claim 199, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, ductal carcinoma *in situ*, lobular carcinoma *in situ*, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

201. (New) The method of claim 199, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is tamoxifen-refractory or tamoxifen resistant.

REMARKS

Please cancel claims 1-157 and add new claims 158-201. Support for the new claims can be found throughout the originally filed application. Accordingly, no new matter has been added by the addition of these new claims. Please enter this amendment prior to substantive examination.

Exemplary Support for Claim Amendments

Claim	Exemplary Support in US 18/128,536
Claim 158	Original Claims 1, 2, and 36, and paragraphs [0150]-[0153] and [0184]
Claim 159	Paragraphs [0185] and [0317]
Claim 160	Paragraph [0259]
Claim 161	Paragraph [0214]
Claim 162	Paragraphs [0195] and [0196]
Claim 163	Paragraphs [0195] and [0196]
Claim 164	Paragraph [0215]
Claim 165	Paragraph [0199]
Claim 166	Paragraph [0195]
Claim 167	Paragraph [0195]
Claim 168	Paragraph [0195]
Claim 169	Paragraph [0432]
Claim 170	Paragraph [0432]
Claim 171	Paragraphs [0206], [0207], and [0432]
Claim 172	Paragraphs [0206] and [0432]
Claim 173	Table 12 and paragraph [0431]
Claim 174	Paragraph [0225]
Claim 175	Paragraph [0226]
Claim 176	Paragraph [0228]
Claim 177	Paragraph [0196]
Claim 178	Paragraph [0201]
Claim 179	Paragraph [0201]

Claim	Exemplary Support in US 18/128,536
Claim 180	Paragraph [0205]
Claim 181	Paragraph [0206]
Claim 182	Paragraph [0206]
Claim 183	Paragraph [0291]
Claim 184	Paragraph [0292]
Claim 185	Paragraph [0223], [0224], and [0267]
Claim 186	Paragraph [0263] and [0350]
Claim 187	Original claims 1 and 2, and paragraphs [0099], [0190], and [0195]
Claim 188	Paragraphs [0206], [0207], and [0432]
Claim 189	Original claims 1, 2, and 36 and paragraph [0190]
Claim 190	Paragraph [0292]
Claim 191	Paragraph [0223], [0224], and [0267]
Claim 192	Paragraph [0263] and [0350]
Claim 193	Paragraph [0352]
Claim 194	Paragraph [0248], [0253], and [0261]
Claim 195	Paragraph [0226]
Claim 196	Paragraph [0228]
Claim 197	Paragraph [0224] and Table 17
Claim 198	Paragraph [0472] and Table 19C
Claim 199	Original claim 44
Claim 200	Original claim 45
Claim 201	Original claim 47

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicant believes no fee is due with this response. However, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 07-1896.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-839-4805.

Respectfully submitted,

Dated: August 4, 2023

/Erin M. Gaffney/

Erin M. Gaffney, Ph.D.
Reg. No. 81,479

DLA PIPER LLP (US)
701 Fifth Avenue, Suite 6900
Seattle, Washington 98104-7029
Tel: (206) 839-4800
Fax (206) 839-4801

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	Steven C. Quay et al.	Group Art Unit:	Unassigned
Serial Number:	18/128,536	Examiner:	Unassigned
Filing or 371 (c) Date:	March 30, 2023	**CONFIRMATION NO:**	**1025**
Title:	METHODS FOR MAKING AND USING ENDOXIFEN	CUST. NO.:	187495

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

ACTIVE\1602047261.1

A. ☒ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☒ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of $260.00 or $104.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $260.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

ACTIVE\1602047261.1

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

ACTIVE\1602047261.1

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 07-1896 (Docket No. 438558-758053).

Respectfully submitted,

Dated: August 4, 2023

/Erin M. Gaffney/

Erin M. Gaffney, Ph.D.
Registration No. 81,479

DLA PIPER LLP (US)
701 Fifth Avenue, Suite 6900
Seattle, Washington 98104-7029
Tel: (206) 839-4800
Fax (206) 839-4801
CUSTOMER NO.: 187495

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	Steven C. Quay et al.	Group Art Unit:	Unassigned
Serial Number:	18/128,536	Examiner:	Unassigned
Filing or 371 (c) Date:	March 30, 2023	**CONFIRMATION NO:**	**1025**
Title:	METHODS FOR MAKING AND USING ENDOXIFEN	CUST. NO.:	187495

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

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The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

ACTIVE\1602047289.1

A. ☒ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☒ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☐ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☐ a fee of $260.00 or $104.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $260.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

ACTIVE\1602047289.1

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☐ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

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-- OR --

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-- AND/OR --

☐ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☒ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☒ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: 18/090,757

Information Disclosure Statement(s) filed on: 01/27/2023

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AND

☒ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $0.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 07-1896 (Docket No. 438558-758053).

Respectfully submitted,

Dated: August 4, 2023

/Erin M. Gaffney/

Erin M. Gaffney, Ph.D.
Registration No. 81,479

DLA PIPER LLP (US)
701 Fifth Avenue, Suite 6900
Seattle, Washington 98104-7029
Tel: (206) 839-4800
Fax (206) 839-4801
CUSTOMER NO.: 187495

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	001	US-11680036	06-20-2023	STEVEN; C. Quay et al.	
	002	US-20060280795-A1	12-14-2006	PENHASI; Adel et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	WO-2016187122-A1	11-24-2016	UNIV IOWA RES FOUND [US]		☒

Examiner Signature		Date Considered	

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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Application Number	18/128,536
				Filing Date	03-30-2023
				First Named Inventor	QUAY; Steven C.
				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	2	of	3	Attorney Docket Number	438558-758053

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
		None	☐

Examiner Signature		Date Considered	

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				First Named Inventor	QUAY; Steven C.
				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	3	of	3	Attorney Docket Number	438558-758053

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Erin M. Gaffney/	Date (YYYY-MM-DD)	2023-08-04
Name/Print	Erin M. Gaffney, Ph.D.	Registration Number	81,479

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 1 of 20

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Attorney Docket Number	438558-758053

U. S. PATENT DOCUMENTS

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	001	US-3848030-A	11-12-1974	VITERBO; R. et al.	
	002	US-4851433-A	07-25-1989	KRAUS; Hans A.	
	003	US-6774122-B2	08-10-2004	EVANS et al.	
	004	US-7384418-B2	06-10-2008	HUNG et al.	
	005	US-7485623-B2	02-03-2009	BUA; Jay	
	006	US-7507769-B2	03-24-2009	NESTOUR; Elisabeth Le	
	007	US-7531578-B2	05-12-2009	FORMAN et al.	
	008	US-7704516-B2	04-27-2010	DROUIN et al.	
	009	US-7705159-B2	04-27-2010	MACDONALD et al.	
	010	US-7786172-B2	08-31-2010	DE; Lignieres et al.	
	011	US-7968532-B2	06-28-2011	LE; Nestour et al.	
	012	US-8048927-B2	11-01-2011	LE NESTOUR; Elisabeth	
	013	US-8058302-B2	11-15-2011	SOLANKI et al.	
	014	US-8063249-B1	11-22-2011	KUSHNER et al.	
	015	US-8119695-B2	02-21-2012	FORMAN et al.	
	016	US-8329680-B2	12-11-2012	EVANS et al.	
	017	US-8436029-B2	05-07-2013	HICKEY et al.	
	018	US-8454945-B2	06-04-2013	McCOOK et al.	
	019	US-8466139-B2	06-18-2013	EVANS et al.	
	020	US-8822511-B2	09-02-2014	COMBS et al.	
	021	US-8993605-B2	03-31-2015	COMBS et al.	
	022	US-9073875-B2	07-07-2015	BOYALL et al.	
	023	US-9090640-B2	07-28-2015	BIERBACH et al.	
	024	US-9200045-B2	12-01-2015	LIU et al.	
	025	US-9220680-B2	12-29-2015	PERUMAL et al.	

Examiner Signature		Date Considered	

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Sheet 2 of 20

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Examiner Name	Unassigned
Attorney Docket Number	438558-758053

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	026	US-9308181-B2	04-12-2016	KISAK et al.	
	027	US-9333190-B2	05-10-2016	AHMAD et al.	
	028	US-11261151-B2	03-01-2022	QUAY et al.	
	029	US-11572334	02-07-2023	QUAY; Steven C. et al.	
	030	US-20020025543-A1	02-28-2002	SERRERO; Ginette	
	031	US-20030021787-A1	01-30-2003	HUNG; David et al.	
	032	US-20030099694-A1	05-29-2003	CEVC; Gregor et al.	
	033	US-20040092894-A1	05-13-2004	HUNG; David et al.	
	034	US-20070059288-A1	03-15-2007	DINSMORE; Jonathan H. et al.	
	035	US-20070161063-A1	07-12-2007	LOVE; Susan et al.	
	036	US-20070190019-A1	08-16-2007	GUO; Chunfeng et al.	
	037	US-20080138391-A1	06-12-2008	CARRARA; Dario Norberto et al.	
	038	US-20080319092-A1	12-25-2008	SINGH; Jagat	
	039	US-20090068190-A1	03-12-2009	BORTZ; Jonathan David	
	040	US-20090098069-A1	04-16-2009	VACCA; Rita Downard	
	041	US-20090208944-A1	08-20-2009	GOETZ; Matthew P. et al.	
	042	US-20090281063-A1	11-12-2009	INAGI; Toshio et al.	
	043	US-20090291102-A1	11-26-2009	FORTIN; Samuel	
	044	US-20090291134-A1	11-26-2009	AHMAD; Ateeq et al.	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 3 of 20

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	045	US-20100015195-A1	01-21-2010	JAIN; Rajesh et al.	
	046	US-20100015200-A1	01-21-2010	McCLAIN; James B. et al.	
	047	US-20100069781-A1	03-18-2010	JOHANSEN; Jerald A. et al.	
	048	US-20100098659-A1	04-22-2010	WATSON; Richard L. et al.	
	049	US-20100112041-A1	05-06-2010	AHMAD; Ateeq et al.	
	050	US-20120010245-A1	01-12-2012	MASINI-ETEVE; Valerie	
	051	US-20120149761-A1	06-14-2012	QUAY; Steven C.	
	052	US-20120164075-A1	06-28-2012	AHMAD; Ateeq et al.	
	053	US-20120301541-A1	11-29-2012	HARONSKY; Elina et al.	
	054	US-20130046171-A1	02-21-2013	JOHANSEN; Jerald A. et al.	
	055	US-20130177590-A1	07-11-2013	COMBS; Andrew P. et al.	
	056	US-20130197087-A1	08-01-2013	SCHLOTZER; Ewald et al.	
	057	US-20140088059-A1	03-27-2014	PERUMAL; Omathanu P. et al.	
	058	US-20140193334-A1	07-10-2014	BIERBACH; Ulrich et al.	
	059	US-20140199391-A1	07-17-2014	BIRBARA; Philip J.	
	060	US-20150080339-A1	03-19-2015	WANG; Guangdi et al.	
	061	US-20150132388-A1	05-14-2015	ANGI; Erzsebet Reka et al.	

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 4 of 20

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	062	US-20150141391-A1	05-21-2015	CHINNAIYAN; Arul M. et al.	
	063	US-20150250802-A1	09-10-2015	LABRIE; Fernand et al.	
	064	US-20160346230-A1	12-01-2016	AHMAD; Ateeq et al.	
	065	US-20160375234-A1	12-29-2016	QUAY; Steven C.	
	066	US-20170145515-A1	05-25-2017	CHEN; Shu-Chih et al.	
	067	US-20170304232-A1	10-26-2017	KHAN; Seema Ahsan et al.	
	068	US-20180049999-A1	02-22-2018	QUAY; Steven C.	
	069	US-20180200206-A1	07-19-2018	QUAY; Steven C.	
	070	US-20190269697-A1	09-05-2019	LABRIE; Fernand	
	071	US-20200207704-A1	07-02-2020	QUAY; Steven C. et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	CN-101891635-A	11-24-2010	YANGTZE RIVER PHARMACEUTICAL GROUP., et al.		☒
	002	CN-102448467-A	05-09-2012	LITHERA INC.		☒
	003	CN-104203961-A	12-10-2014	XAVIER UNIVERSITY.		☒

Examiner Signature		Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 5 of 20

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
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FOREIGN PATENT DOCUMENTS

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	004	CN-104230723-B	08-24-2016	ASYMCHEM LAB TIANJIN CO LTD.		☒
	005	CN-104352504-A	02-18-2015	ENDORECH INC.		☒
	006	CN-105579044-A	05-11-2016	DEL MAR PHARMACEUTICALS., et al.		☒
	007	EP-1709062-B9	02-13-2013	CEDARBURG PHARMACEUTICALS INC [US]		☐
	008	EP-2350111-A1	08-03-2011	SYNTHON BV [NL]		☐
	009	EP-3202420-A1	08-09-2017	BESINS HEALTHCARE LU SARL [LU]		☐
	010	EP-3202420-B1	03-04-2020	BESINS HEALTHCARE LU SARL [LU]		☐
	011	WO-0064416-A3	03-08-2001	LILLY CO ELI [US], et al.		☐
	012	WO-0174366-A1	10-11-2001	ASTRAZENECA AB [SE], et al.		☐
	013	WO-2008066783-A2	06-05-2008	ARIAD GENE THERAPEUTICS INC [US], et al.		☐
	014	WO-2008070463-A2	06-12-2008	JINA PHARMACEUTICALS INC [US], et al.		☐

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Sheet 6 of 20

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	015	WO-2008070463-A9	09-18-2008	JINA PHARMACEUTICALS INC [US], et al.		☐
	016	WO-2009032699-A1	03-12-2009	DRUGTECH CORP [US], et al.		☐
	017	WO-2009069140-A1	06-04-2009	DABUR PHARMA LTD [IN], et al.		☐
	018	WO-2009120999-A2	10-01-2009	OLEMA PHARMACEUTICALS INC [US], et al.		☐
	019	WO-2009120999-A3	12-30-2009	OLEMA PHARMACEUTICALS INC [US], et al.		☐
	020	WO-2010066810-A1	06-17-2010	BESINS HEALTHCARE [BE], et al.		☐
	021	WO-2010135703-A2	11-25-2010	JINA PHARMACEUTICALS INC [US], et al.		☐
	022	WO-2011072244-A1	06-16-2011	SINAI SCHOOL MEDICINE [US], et al.		☐
	023	WO-2012050263-A1	04-19-2012	CJ CHEILJEDANG CORP [KR], et al.		☐
	024	WO-2013050280-A1	04-11-2013	COMMISSARIAT ENERGIE ATOMIQUE [FR]		☒
	025	WO-2013134230-A1	09-12-2013	XAVIER UNIVERSITY [US]		☐

Examiner Signature		Date Considered	

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	026	WO-2014060640-A8	05-07-2015	FERMION OY [FI]		☐
	027	WO-2014134165-A1	09-04-2014	SLOAN KETTERING INST CANCER [US]		☐
	028	WO-2014141292-A2	09-18-2014	INTAS PHARMACEUTICALS LTD [IN]		☐
	029	WO-2015106094-A1	07-16-2015	ATOSSA GENETICS INC [US]		☐
	030	WO-2015138340-A1	09-17-2015	REPROS THERAPEUTICS INC [US]		☐
	031	WO-2015187727-A2	12-10-2015	ATOSSA GENETICS INC [US]		☐
	032	WO-2016168021-A1	10-20-2016	ATOSSA GENETICS INC [US]		☐
	033	WO-2017011623-A1	01-19-2017	ATOSSA GENETICS INC [US]		☐
	034	WO-2017070651-A1	04-27-2017	US HEALTH [US], et al.		☐
	035	WO-2017080770-A1	05-18-2017	ROBERT BOSCH GES FÜR MEDIZINISCHE FORSCHUNG MBH [DE]		☒
	036	WO-2019051368-A1	03-14-2019	ATOSSA GENETICS INC [US]		☐

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Sheet 8 of 20

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Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	037	WO-2019051370-A1	03-14-2019	ATOSSA GENETICS INC [US]		☐
	038	WO-2019051416-A1	03-14-2019	ATOSSA GENETICS INC [US]		☐

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Sheet 9 of 20

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NON-PATENT LITERATURE DOCUMENTS			
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	001	ACKERMAN A.B., et al., "Contrary View: The Breast is not an Organ Per Se, but a Distinctive Region of Skin and Subcutaneous Tissue," The American Journal of Dermatopathology, April 2007, Vol. 29 (2), pp. 211-218.	☐
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Sheet 10 of 20

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	010	BERNHARD H., et al., "Adoptive Transfer of Autologous, HER2-Specific, Cytotoxic T Lymphocytes for the Treatment of HER2-Overexpressing Breast Cancer," Cancer Immunology, Immunotherapy, 2008, Vol. 57, pp. 271-280.	☐
	011	BHATNAGAR P., et al., "Tumor Lysing Genetically Engineered T Cells Loaded with Multi-Modal Imaging Agents," SCIENTIFIC REPORTS, Vol. 4, No. 4502, DOI: 10.1038/srep04502, published on March 28, 2014, 21 pages.	☐
	012	CHANG M., "Tamoxifen Resistance in Breast Cancer," Biomolecules Therapeutics, May 2012, Vol. 20 (3), pp. 256-267.	☐
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Sheet 11 of 20

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	019	Extended European Search Report for EP Application EP17857260.8, dated 24 March 2020, 16 pages.	☐
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	021	FASCHING P.A., et al., "Ki67, Chemotherapy Response and Prognosis in Breast Cancer Patients receiving Neoadjuvant Treatment," BMC Cancer, Vol. 11, Article 486, 2011, 13 pages.	☐
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	028	GOETZ M.P., et al., "A First-in-Human Phase I Study of the Tamoxifen (TAM) Metabolite, Z-Endoxifen Hydrochloride (Z-Endx) in Women with Aromatase Inhibitor (AI) Refractory Metastatic Breast Cancer (MBC) (NCT01327781)," San Antonio Breast Conference, December 2013, PD3-4, 4 pages.	☐
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Sheet 13 of 20

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	035	IKEDA H., et al., "Combination Treatment with Fulvestrant and various Cytotoxic Agents (Doxorubicin, Paclitaxel, Docetaxel, Vinorelbine, and 5-Fluorouracil) has a Synergistic Effect in Estrogen Receptor-Positive Breast Cancer," Cancer Science, Vol. 102 (11), November 2011, pp. 2038-2042, 5 Pages.	☐
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	044	JORDAN, C. New insights into the metabolism of tamoxifen and its role in the treatment and prevention of breast cancer. Steroids. 2007 Nov; 72(13): 829-842.	☐

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	045	Journal of Pharmaceutical Science and Technology, Japan, 2006, Vol. 66, No. 6, pp. 435-439. (No English Translation available. Document showing a well-known technique).	☐
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	Filing Date	03-30-2023
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	055	LEHMANN, "Identification of Human Triple-Negative Breast Cancer Subtypes and Preclinical Models for Selection of Targeted Therapies," Journal of Clinical Invest, Vol. 121 (7), 2011, pp.2750-2767.	☐
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	061	MAHONEY M.E., et al., "Intraductal Therapy of Ductal Carcinoma In Situ: A Presurgery Study," Clinical Breast Cancer, August 2013, 13(4), pp. 280-286.	☐
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	064	MAXIMOV P.Y., et al., "Structure-Function Relationships of Estrogenic Triphenylethylenes Related to Endoxifen and 4- Hydroxytamoxifen," Journal of Medicinal Chemistry, 22 April 2010, Vol. 53 (8), pp. 3273-3283.	☐
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	066	MEMORIAL SLOAN KETTERING: “T-Cell Therapy for Advanced Breast Cancer,” 2016, pp. 1-8.	☐
	067	MILLER, et al., "Stereospecific Synthesis of (Z)-Tamoxifen via Carbometallation of Alkynylsilanes," The Journal of Organic Chemistry, Vol. 50 (12), 1985, pp. 2121-2123.	☐
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	070	PARTRIDGE, et al., "Adherence to Initial Adjuvant Anastrozole Therapy among Women with Early Stage Breast Cancer," Journal Clinical Oncology, 01 Febuary 2008, Vol. 26 (4).	☐
	071	PARTRIDGE et al., Nonadherence to Adjuvant Tamoxifen Therapy in Women with Primary Breast Cancer. J. Clinical Oncology, Vol. 21, Feb 15, 2003.	☐
	072	ROBERTSON, et al., "Fulvestrant: Pharmacokinetics and Pharmacology," British Journal of Cancer, 2004, Vol. 90, pp. S7-S10.	☐
	073	ROBERTSON, et al., "Pharmacokinetic Profile of Intramuscular Fulvestrant in Advanced Breast Cancer," Clinical Pharmacokinetics, 2004, Vol. 43 (8), pp. 529-538.	☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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Substitute for form 1449/PTO	Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)	Application Number	18/128,536
	Filing Date	03-30-2023
	First Named Inventor	QUAY; Steven C.
	Art Unit	Unassigned
	Examiner Name	Unassigned
Sheet 17 of 20	Attorney Docket Number	438558-758053

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	074	ROUANET P., et al., "Neoadjuvant Percutaneous 4-Hydroxytamoxifen Decreases Breast Tumoral Cell Proliferation: A Prospective Controlled Randomized Study Comparing Three Doses of 4-hydroxytamoxifen Gel to Oral Tamoxifen," Journal of Clinical Oncology, 1 May 2005, Vol. 23(13), pp. 2980-2987.	☐
	075	SANO, et al., "Short-step Synthesis of Droloxifene via the Three-Component Coupling Reaction among Aromatic Aldehyde, Cinnamyltrimethylsilane, and 13-Chlorophenetole," Tetrahedron Letters, 6 March 2006, Vol. 47 (10), pp. 1631-1635.	☐
	076	Search Report and Written Opinion for Singapore Patent Application No. SG11202002105W mailed April 21, 2021, 8 pages.	☐
	077	SOLTAMOX Oral Solution, Rx Only, Savient Pharmaceuticals, Inc, 25 August 2005, 37 pages.	☐
	078	STEARNS, et al., "Preclinical and Clinical Evaluation of Intraductally Administered Agents in Early Breast Cancer," Science Translational Medicine, Oct. 26, 2011, Vol. 3 (106), 19 pages, 106ra108.	☐
	079	SUN M., et al., "Construction and Evaluation of a Novel Humanized HER2-Specific Chimeric Receptor," Breast Cancer Research, 2014, Vol. 16:R61, 10 pages.	☐
	080	Taiwanese Patent Application No. 107131790 Search Report dated June 30, 2022. English Translation included.	☒
	081	UMAREDDY, et al., "Improved Process for Centchroman, A Selective Estrogen Receptor Modulator (SERM)," Journal of Chemical and Pharmaceutical Research, 2015, Vol. 7 (7), pp. 736-741.	☐
	082	UMAREDDY, et al., "Total Synthesis of Lasofoxifene and Nafoxidine," An International Journal for Rapid Communication of Synthetic Organic Chemistry, 2016, Vol. 46 (4), pp. 309-313.	☐
	083	VERGOTE, et al., "Fulvestrant is an Effective and Well-Tolerated Endocrine Therapy for Postmenopausal Women with Advanced Breast Cancer," Results from Clinical Trials, British Journal of Cancer, 90 (Suppl), 2004, pp. S11-S14.	☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 18 of 20

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	084	WELSH, J., "Induction of apoptosis in breast cancer cells in response to vitamin D and antiestrogens", BIOCHEMISTRY AND CELL BIOLOGY, vol. 72, no. 11-12, 1994, pages 537-545, XP009511548, ISSN: 0829-8211.	☐
	085	WU, et al., "Single Cell MicroRNA Analysis using Microftuidic Ftow Cytometry," PLOS One, 2013, Vol. 8 (1), e55044.	☐
	086	WU X., et al., "The Tamoxifen Metabolite, Endoxifen, is a Potent Antiestrogen that Targets Estrogen Receptor Alpha for Degradation in Breast Cancer Cells," Cancer Research, 01 March 2009, Vol. 69(5), , pp. 1722-1727.	☐
	087	YAN YAODONG., "Design and Development of Sustained-Release and Controlled-Release Formulations," Chinese Medicine Science and Technology Publishing House, 30 June 2006 (2006-06-30), pp. 421-428.	☐
	088	YANG Y., et al., "Dendron-Based Micelles for Topical Delivery of Endoxifen: A Potential Chemo-Preventive Medicine for Breast Cancer," Advanced Functional Materials, 2014, Vol. 24, pp. 2442-2449.	☐
	089	YAO, et al., "Synthesis and Reactivity of Potential Toxic Metabolites of Tamoxifen Analogues: Droloxifene and Toremifene a-Quinones," Chemical Research in Toxicology, 2001, Vol. 14 (12), pp. 1643-1653.	☐
	090	YONEYA, et al., "Thiochroman Derivative CH4986399, A New Nonsteroidal Estrogen Receptor Down-regulator, Is effective in Breast Cancer Models," Anticancer Research, 2010, Vol. 30, pp. 873-878.	☐
	091	ZHANG B., et al., "The Safety Parameters of the Study on Intraductal Cytotoxic Agent Delivery to the Breast Before Mastectomy," http://dx.doi.Org/10.3978/j.issn.1000-9604.2014.10.06 , September 09, 2014, Chinese Journal of Cancer Research, Vol. 26(5), pp: 579-587.	☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 19 of 20

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	092	ZHAO Y., et al., "A Herceptin-Based Chimeric Antigen Receptor with Modified Signaling Domains Leads to Enhanced Survival of Transduced T Lymphocytes and Antitumor Activity," The Journal of Immunology, https://www.researchgate.net/publication/38024914 , November, 2009, Vol. 183(9), pp: 5563-5574.	☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Application Number	18/128,536
				Filing Date	03-30-2023
				First Named Inventor	QUAY; Steven C.
				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	20	of	20	Attorney Docket Number	438558-758053

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Erin M. Gaffney/	Date (YYYY-MM-DD)	2023-08-04
Name/Print	Erin M. Gaffney, Ph.D.	Registration Number	81,479

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ACTIVE\1602046879.1

Electronic Patent Application Fee Transmittal

Application Number:	18128536
Filing Date:	30-Mar-2023
Title of Invention:	METHODS FOR MAKING AND USING ENDOXIFEN
First Named Inventor/Applicant Name:	Steven C. Quay
Filer:	Erin Gaffney/Christina Campbell
Attorney Docket Number:	438558-758053

Filed as Small Entity

Filing Fees for Utility under 35 USC 111(a)

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
UTILITY FILING FEE (ELECTRONIC FILING)	4011	1	64	64
UTILITY SEARCH FEE	2111	1	280	280
UTILITY EXAMINATION FEE	2311	1	320	320
Pages:				
UTILITY APPL SIZE FEE PER 50 SHEETS >100	2081	1	168	168
Claims:				
CLAIMS IN EXCESS OF 20	2202	24	40	960
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
LATE FILING FEE FOR OATH OR DECLARATION	2051	1	64	64
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	2251	1	88	88
Miscellaneous:				
		Total in USD ($)		**1944**

Electronic Acknowledgement Receipt

EFS ID:	48398215
Application Number:	18128536
International Application Number:	
Confirmation Number:	1025
Title of Invention:	METHODS FOR MAKING AND USING ENDOXIFEN
First Named Inventor/Applicant Name:	Steven C. Quay
Customer Number:	187495
Filer:	Erin Gaffney/Christina Campbell
Filer Authorized By:	Erin Gaffney
Attorney Docket Number:	438558-758053
Receipt Date:	04-AUG-2023
Filing Date:	30-MAR-2023
Time Stamp:	16:46:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	DA
Payment was successfully received in RAM	$1944
RAM confirmation Number	E202384G48208710
Deposit Account	071896
Authorized User	Christina Campbell
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: 37 CFR 1.16 (National application filing, search, and examination fees) 37 CFR 1.17 (Patent application and reexamination processing fees)	

37 CFR 1.19 (Document supply fees)

37 CFR 1.20 (Post Issuance fees)

37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Applicant Response to Pre-Exam Formalities Notice	438558-758053-response-ntfmp.pdf	116188 b0f2dc35c7b8e23c55550cdd37b9afe37fc9b884	no	2
Warnings:					
Information:					
2		438558-758053-prelim.pdf	210346 287073156928 3f7406b9060108f79e47d7630874	yes	9
	Multipart Description/PDF files in .zip description				
	Document Description		**Start**	**End**	
	Preliminary Amendment		1	1	
	Claims		2	6	
	Applicant Arguments/Remarks Made in an Amendment		7	9	
Warnings:					
Information:					
3	Transmittal Letter	438558-758053-transmittal.pdf	157360 58f0b2e7427f10a66d9c2fb532d590914ec78e25	no	4
Warnings:					
Information:					
4	Transmittal Letter	438558-758053-transmittal-box-h.pdf	157433 3d87ca8ab2018e5603fbdc36e8a4cc9f36afb35c	no	4
Warnings:					
Information:					
5	Information Disclosure Statement (IDS) Form (SB08)	438558-758053_IDS_SB08_20230803140036.pdf	133919 31b6b0ffb39b23de943ac9e1d5e9a944aec03a0d	no	3

Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
6	Information Disclosure Statement (IDS) Form (SB08)	438558-758053_IDS_SB08_20230803140036_Box_H.pdf	312056 ebdd6d282802bb54bd16e5664bea5e3410fd7633	no	20
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
7	Foreign Reference	WO2016187122A1_EFS.pdf	6187328 e75c20b82ed359f11b58fb387cdf42b9d1822def	no	100
Warnings:					
Information:					
8	Fee Worksheet (SB06)	fee-info.pdf	53697 477970030e9410d3a1b2b3e2667f2d731a6ee077	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	7328327		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on August 4, 2023

DLA PIPER LLP (US)

By: /Christina Campbell/

Attorney Docket No.: 438558-758053

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Confirmation No.: 1025
Steven C. Quay et al.	
Application No.: 18/128,536	Examiner: Unassigned
Filed: March 30, 2023	Art Unit: Unassigned
For: METHODS FOR MAKING AND USING ENDOXIFEN	RESPONSE TO NOTICE TO FILE MISSING PARTS
Customer No.: 187495	

Mail Stop Missing Parts
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Pursuant to the Notice to File Missing Parts of Non-Provisional Application, dated May 4, 2023, enclosed are the following to be made of record in the above-identified application:

1) Preliminary Amendment
2) Information Disclosure Statement

Intas Exhibit 1002
Page 225 of 408
PGR2025-00043

Please charge Deposit Account No. 07-1896 for the following fees:

Small Entity:	(a)	Filing Fee	$64
	(b)	Search Fee	$280
	(c)	Examination Fee	$320
	(d)	Missing Parts Surcharge	$64
	(e)	One Month Extension of Time Fee	$88
	(f)	24 claims over 20	$960
	(g)	36 pages in excess of 100 application size fee	$168
	TOTAL FEES TO BE CHARGED		$1,944

The Commissioner is hereby authorized to charge any additional fees associated with this paper or during the pendency of this application, or credit any overpayment, to Deposit Account No. 07-1896.

Respectfully submitted,

Dated: August 4, 2023

/Erin M. Gaffney/

Erin M. Gaffney, Ph.D.
Reg. No. 81,479

DLA PIPER LLP (US)
701 Fifth Avenue, Suite 6900
Seattle, Washington 98104-7029
Tel: (206) 839-4800
Fax (206) 839-4801

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
18/128,536	03/30/2023		1856	438558-758053	44	2

CONFIRMATION NO. 1025

UPDATED FILING RECEIPT

187495
DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

Date Mailed: 08/10/2023

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Steven C. Quay, Seattle, WA;
Yao-Lin Sun, Tainan City, TAIWAN;
LungHu Wang, Kaohsiung City, TAIWAN;
ChangJung Wu, Kaohsiung City, TAIWAN;
ChuanDer Huang, Tainan City, TAIWAN;

Applicant(s)

Atossa Therapeutics, Inc., Seattle, WA;

Power of Attorney: The patent practitioners associated with Customer Number 187495

Domestic Priority data as claimed by applicant

This application is a CON of 18/090,757 12/29/2022 PAT 11,680,036
which is a CON of 17/580,428 01/20/2022 PAT 11,572,334
which is a CON of 16/641,985 02/25/2020 PAT 11,261,151
which is a 371 of PCT/US18/50272 09/10/2018
which claims benefit of 62/693,885 07/03/2018
and claims benefit of 62/624,787 01/31/2018
and claims benefit of 62/556,799 09/11/2017
and claims benefit of 62/556,884 09/11/2017

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 05/02/2023

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/128,536**

Projected Publication Date: 11/16/2023

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

METHODS FOR MAKING AND USING ENDOXIFEN

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign

patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

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The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET Substitute for Form PTO-1360 (For use with Form PTO/SB/06)	Application Number 18/128,536	Filing Date
	Applicant(s) Steven C. Quay	

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
1	1					
2		1				
3		1				
4		1				
5		1				
6		2				
7		1				
8		(1)				
9		(1)				
10		(1)				
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51		(1)				
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100	1					

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET Substitute for Form PTO-1360 (For use with Form PTO/SB/06)	Application Number 18/128,536	Filing Date
	Applicant(s) Steven C. Quay	

* May be used for additional claims or amendments

CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT	
	Indep	Depend	Indep	Depend	Indep	Depend
101		(1)				
102		(1)				
103		(1)				
104		(1)				
105		(1)				
106		(1)				
107		(1)				
108		(1)				
109		(1)				
110		(1)				
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121	1					
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131		(1)				
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133		(1)				
134		(1)				
135	1					
136		1				
137		2				
138		(1)				
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147		(1)				
148		(1)				
149		(1)				
150		(1)				
Total Indep	8					
Total Depend	161	↵		↵		↵
Total Claims			0		0	

CLAIMS	*		*		*	
	Indep	Depend	Indep	Depend	Indep	Depend
151	1					
152		1				
153		2				
154		(1)				
155		(1)				
156		(1)				
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 18/128,536

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	64		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	280		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	320		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	44 minus 20 =	* 24	x 40 =	960	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	*	x =	0			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			168			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	832		TOTAL	

APPLICATION AS AMENDED - PART II

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
AMENDMENT A	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
AMENDMENT B	Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
	Application Size Fee (37 CFR 1.16(s))									
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

Doc code: PET.OP.AGE
Description: Petition to make special based on age/health

PTO/SB/130 (01-19)
Approved for use through 11/30/2020. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number

PETITION TO MAKE SPECIAL BASED ON AGE FOR ADVANCEMENT OF EXAMINATION UNDER 37 CFR 1.102(c)(1)

Application Information

Application Number	18/128,536	Confirmation Number	1025	Filing Date	2023-03-30
Attorney Docket Number (optional)	438558-758053	Art Unit	1629	Examiner	Unassigned
First Named Inventor	Steven C. Quay				
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN				

Attention: Office of Petitions

An application may be made special for advancement of examination upon filing of a petition showing that the applicant is 65 years of age, or more. No fee is required with such a petition. See 37 CFR 1.102(c)(1) and MPEP 708.02 (II).

APPLICANT HEREBY PETITIONS TO MAKE SPECIAL FOR ADVANCEMENT OF EXAMINATION IN THIS APPLICATION UNDER 37 CFR 1.102(c)(1) and MPEP 708.02 (II) ON THE BASIS OF THE APPLICANT'S AGE.

A grantable petition requires one of the following items:

(1) Statement by one named inventor in the application that he/she is 65 years of age, or more; or

(2) Certification by a registered attorney/agent having evidence such as a birth certificate, passport, driver's license, etc. showing one named inventor in the application is 65 years of age, or more.

Name of inventor who is 65 years of age, or older

Given Name	Middle Name	Family Name	Suffix
Steven	C.	Quay	

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 11.18. Please see 37 CFR 1.4(d) for the format of the signature.

Select (1) or (2):

☐ (1) I am an inventor in this application and I am 65 years of age, or more.

☒ (2) I am an attorney or agent registered to practice before the Patent and Trademark Office, and I certify that I am in possession of evidence, and will retain such in the application file record, showing that the inventor listed above is 65 years of age, or more.

Signature	/Erin M. Gaffney/	Date (YYYY-MM-DD)	2023-08-15
Name	Erin M. Gaffney, Ph.D.	Registration Number	81,479

This collection of information is required by 37 CFR 1.102(c)(1). The information is required to obtain or retain a benefit by the public, which is to file (and by the USPTO to process) a petition to make special based on age for advancement of examination. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 2 hours to complete, including gathering, preparing, and submitting the completed form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND COMPLETED FORMS TO THE CHIEF INFORMATION OFFICER. **Submit completed forms electronically over EFS-Web, or mail to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a (m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	48445167
Application Number:	18128536
International Application Number:	
Confirmation Number:	1025
Title of Invention:	METHODS FOR MAKING AND USING ENDOXIFEN
First Named Inventor/Applicant Name:	Steven C. Quay
Customer Number:	187495
Filer:	Erin Gaffney/Christina Campbell
Filer Authorized By:	Erin Gaffney
Attorney Docket Number:	438558-758053
Receipt Date:	15-AUG-2023
Filing Date:	30-MAR-2023
Time Stamp:	18:35:13
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Petition to make special based on Age/ Health	438558-758053-petition.pdf	204447 62609bfa7570ca88f53125b1860ab644d3236f09	no	2
Warnings:					

Information:	
Total Files Size (in bytes):	204447

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.
National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.
New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/128,536	03/30/2023	Steven C. Quay	438558-758053	1025

187495 7590 09/21/2023

DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

EXAMINER	
CENTRAL, DOCKET	

ART UNIT	PAPER NUMBER
OPAP	

NOTIFICATION DATE	DELIVERY MODE
09/21/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

seattlepatentdocket@us.dlapiper.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

In re Application of	:	
Quay et al.	:	
Application No. 18/128,536	:	DECISION ON PETITION
Filed: March 30, 2023	:	
For: METHODS FOR MAKING AND USING ENDOXIFEN	:	

This is a decision on the petition under 37 CFR 1.102(c)(1), filed August 15, 2023, to make the above-identified application special based on applicant's age as set forth in MPEP § 708.02, Section II.

The petition is **GRANTED**.

A grantable petition to make an application special under 37 CFR 1.102(c)(1) and MPEP § 708.02, Section II: Applicant's Age, must be accompanied by evidence showing that the applicant is 65 years of age, or more, such as applicant's statement or a statement from a registered practitioner that he or she has evidence that the applicant is 65 years of age or older. No fee is required.

The instant petition includes a statement from the registered attorney or agent attesting to having evidence of the inventor's age being 65 years of age or more. Accordingly, the above-identified application has been accorded "special" status.

Inquiries concerning this decision should be directed to Paralegal Specialist Lara Willsey at 571-270-1501. All other inquiries concerning the examination or status of the application are accessible in the Patent Electronic Filing System.[1]

/JOANNE L BURKE/
Lead Paralegal Specialist, OPET

[1] https://www.uspto.gov/patents/apply (for help using Patent Electronic Filing System call the Patent Electronic Business Center at (866) 217-9197).

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/128,536	**11/09/2023 08:02:01 PM Z ET**	**438558-758053**

Title of Invention

METHODS FOR MAKING AND USING ENDOXIFEN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1025	FILED BY	Christina Campbell
PATENT CENTER #	63213494	FILING DATE	03/30/2023
CUSTOMER #	187495	FIRST NAMED INVENTOR	Steven C. Quay
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Erin Gaffney

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
438558-758053-Petition.pdf	2	Request for Express Abandonment for refund or to avoid publication	195 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
438558-758053-Petition.pdf	9933BDB2CE827A782CE0E5A31B003BD317C9E0457C051D710135F68997FAC9EDD9648881AC23FB317164EE607C5253495A0297F3415833FE2BDF872BD3BC287D

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/128,536	**11/09/2023 08:02:01 PM Z ET**	**438558-758053**

Title of Invention

METHODS FOR MAKING AND USING ENDOXIFEN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1025	FILED BY	Christina Campbell
PATENT CENTER #	63213494	AUTHORIZED BY	Erin Gaffney
CUSTOMER #	187495	FILING DATE	03/30/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Steven C. Quay

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 071896	E2023A9K03089104	Christina Campbell

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
071896	37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2464	PETITIONS REQUIRING THE PETITION FEE SET FORTH IN 37 CFR 1.17(H) (GROUP III)	56.00	1	56.00
			TOTAL AMOUNT:	**$56.00**

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement

Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: PGEA
Document Description: Request for Express Abandonment for refund or to avoid publication

PTO/AIA/24A (05-22)
Approved for use through 06/30/2024. OMB 0651-0059
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PETITION FOR EXPRESS ABANDONMENT TO AVOID PUBLICATION UNDER 37 CFR 1.138(c)

File the petition electronically using USPTO's patent electronic filing system (Patent Center or EFS-Web)
Or **Mail** the petition to:
Mail Stop Express Abandonment
Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Application Number	18/128,536
Filing Date	March 30, 2023
First Named Inventor	Steven C. Quay
Art Unit	1629
Examiner Name	RAYMOND J HENLEY III
Attorney Docket Number	438558-758053

Petition for Express Abandonment to Avoid Publication under 37 CFR 1.138(c)

I hereby petition to expressly abandon the above-identified application to avoid publication.

Petition Fee – must be filed with petition to avoid delays in recognizing the petition.

a. ☒ The Director is hereby authorized to charge the petition fee under 37 CFR 1.17(h) to Deposit Account No. 07-1896.

b. ☐ Check in the amount of $_____ is enclosed.

c. ☐ Payment by credit card (Form PTO-2038 is enclosed).

d. ☒ Payment by USPTO's patent electronic filing system (Patent Center or EFS-Web).

NOTE: A paper requesting express abandonment of an application is not effective unless and until an appropriate USPTO official recognizes and acts on the paper. See the Manual of Patent Examining Procedure (MPEP), section 711.01. In addition, the paper will not stop publication of the application unless a petition under 37 CFR 1.138(c) is recognized and acted on by the Pre-Grant Publication Division in sufficient time to avoid publication (e.g., more than four (4) weeks prior to the projected publication date).

TO REQUEST A REFUND OF SEARCH FEE AND EXCESS CLAIMS FEE (IF ELIGIBLE), PLEASE ALSO INCLUDE FORM PTO/AIA/24B WITH THIS FORM.

I am the:

☐ applicant.

☒ attorney or agent of record. Attorney or agent registration number is 81,479

☐ attorney or agent acting under 37 CFR 1.34, who is authorized under 37 CFR 1.138(b) because the application is expressly abandoned in favor of a continuing application. Attorney or agent registration number is _____.

/Erin M. Gaffney/ — Signature
November 9, 2023 — Date
Erin M. Gaffney, Ph.D. — Typed or printed name
206-839-4805 — Telephone Number

Note: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required, see below.

☐ Total of _____ forms are submitted.

A Federal agency may not conduct or sponsor, and a person is not required to respond to, nor shall a person be subject to a penalty for failure to comply with an information collection subject to the requirements of the Paperwork Reduction Act of 1995, unless the information collection has a currently valid OMB Control Number. The OMB Control Number for this information collection is 0651-0059. Public burden for this form is estimated to average 12 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the information collection. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the Chief Administrative Officer, United States Patent and Trademark Office, P.O. Box 1450, Alexandria, VA 22313-1450 or email InformationCollection@uspto.gov. **DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.** If filing this completed form by mail, send to: **Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	Art Unit
	RAYMOND J HENLEY III	1629

CPC - Searched*		
Symbol	Date	Examiner
A61K 31/135	11/07/2023	RJH

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
514	648	11/07/2023	RJH

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
Reviewed related applications	11/07/2023	RJH
PE2E/PALM applicant/inventor search	11/07/2023	RJH
STN art search, (summary attached)	11/07/2023	RJH

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

/RAYMOND J HENLEY III/ Primary Examiner, Art Unit 1629	

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Page 246 of 408
PGR2025-00043

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	Art Unit
	RAYMOND J HENLEY III	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS										
☐ Claims renumbered in the same order as presented by applicant						☐ CPA		☐ T.D.		☐ R.1.47
CLAIM		DATE								
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	2	-								
	3	-								
	4	-								
	5	-								
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Page 247 of 408
PGR2025-00043

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	**Art Unit**
	RAYMOND J HENLEY III	1629

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
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	Examiner	**Art Unit**
	RAYMOND J HENLEY III	1629

CLAIM		DATE								
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	**Art Unit**
	RAYMOND J HENLEY III	1629

CLAIM		DATE								
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	198	✓								

Intas Exhibit 1002
Page 250 of 408
PGR2025-00043

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	**Art Unit**
	RAYMOND J HENLEY III	1629

CLAIM		DATE								
Final	Original	11/07/2023								
	199	✓								
	200	✓								
	201	✓								

Intas Exhibit 1002
Page 251 of 408
PGR2025-00043

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                D CLUSTER .PHARM .PHARMACEUTICAL
                D SET

     FILE 'REGISTRY' ENTERED AT 09:41:01 ON 07 NOV 2023
L1             0 SEA SPE=ON  ABB=ON  PLU=ON  ENDOTOXIFEN/CN
L2             1 SEA SPE=ON  ABB=ON  PLU=ON  ENDOXIFEN/CN

     FILE 'HCAPLUS' ENTERED AT 09:41:40 ON 07 NOV 2023
L3           635 SEA SPE=ON  ABB=ON  PLU=ON  ENDOXIFEN OR L2
L4         43792 SEA SPE=ON  ABB=ON  PLU=ON  ENTERIC
L5            12 SEA SPE=ON  ABB=ON  PLU=ON  L3 (P) L4
L6            49 SEA SPE=ON  ABB=ON  PLU=ON  Z (W) ENDOXIFEN
L7             4 SEA SPE=ON  ABB=ON  PLU=ON  L5 AND L6

     FILE 'USPATFULL' ENTERED AT 09:42:53 ON 07 NOV 2023
L8            10 SEA SPE=ON  ABB=ON  PLU=ON  L5 AND L6
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Bibliographic Data

Application No: 18/128,536

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /RAYMOND J HENLEY III/ Examiner's Signature | Initials

Title: METHODS FOR MAKING AND USING ENDOXIFEN

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
03/30/2023	514	1629	
RULE			

APPLICANTS

Atossa Therapeutics, Inc.,

INVENTORS

Steven C. Quay, Seattle, WA, UNITED STATES

Yao-Lin Sun, Tainan City, TAIWAN

LungHu Wang, Kaohsiung City, TAIWAN

ChangJung Wu, Kaohsiung City, TAIWAN

ChuanDer Huang, Tainan City, TAIWAN

CONTINUING DATA

This application is a CON of 18090757 12/29/2022 PAT 11680036

18090757 is a CON of 17580428 01/20/2022 PAT 11572334

17580428 is a CON of 16641985 02/25/2020 PAT 11261151

16641985 is a 371 of PCT/US18/50272 09/10/2018

PCT/US18/50272 has PRO of 62693885 07/03/2018

PCT/US18/50272 has PRO of 62624787 01/31/2018

PCT/US18/50272 has PRO of 62556884 09/11/2017

PCT/US18/50272 has PRO of 62556799 09/11/2017

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

05/02/2023

**** SMALL ENTITY ****

STATE OR COUNTRY

UNITED STATES

ADDRESS

FILING FEE RECEIVED

$1,944

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	~~Unassigned~~ 1629
Examiner Name	~~Unassigned~~ R.J. Henley III
Attorney Docket Number	438558-758053

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
/R.J.H/	001	US-11680036	06-20-2023	STEVEN; C. Quay et al.	
/R.J.H/	002	US-20060280795-A1	12-14-2006	PENHASI; Adel et al.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
/R.J.H/	001	WO-2016187122-A1	11-24-2016	UNIV IOWA RES FOUND [US]		☒

Examiner Signature	/RAYMOND J HENLEY III/ (11/07/2023)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

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Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Application Number	18/128,536
				Filing Date	03-30-2023
				First Named Inventor	QUAY; Steven C.
				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	2	of	3	Attorney Docket Number	438558-758053

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
		None	☐

Examiner Signature		Date Considered	

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Substitute for form 1449/PTO				Complete if Known	
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				Filing Date	03-30-2023
				First Named Inventor	QUAY; Steven C.
				Art Unit	Unassigned
				Examiner Name	Unassigned
Sheet	3	of	3	Attorney Docket Number	438558-758053

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Erin M. Gaffney/	Date (YYYY-MM-DD)	2023-08-04
Name/Print	Erin M. Gaffney, Ph.D.	Registration Number	81,479

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 20

Complete if Known	
Application Number	18/128,536
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Art Unit	~~Unassigned~~ 1629
Examiner Name	~~Unassigned~~ R.J. Henley III
Attorney Docket Number	438558-758053

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	001	US-3848030-A	11-12-1974	VITERBO; R. et al.	
	002	US-4851433-A	07-25-1989	KRAUS; Hans A.	
	003	US-6774122-B2	08-10-2004	EVANS et al.	
	004	US-7384418-B2	06-10-2008	HUNG et al.	
	005	US-7485623-B2	02-03-2009	BUA; Jay	
	006	US-7507769-B2	03-24-2009	NESTOUR; Elisabeth Le	
	007	US-7531578-B2	05-12-2009	FORMAN et al.	
	008	US-7704516-B2	04-27-2010	DROUIN et al.	
	009	US-7705159-B2	04-27-2010	MACDONALD et al.	
	010	US-7786172-B2	08-31-2010	DE; Lignieres et al.	
	011	US-7968532-B2	06-28-2011	LE; Nestour et al.	
	012	US-8048927-B2	11-01-2011	LE NESTOUR; Elisabeth	
	013	US-8058302-B2	11-15-2011	SOLANKI et al.	
	014	US-8063249-B1	11-22-2011	KUSHNER et al.	
	015	US-8119695-B2	02-21-2012	FORMAN et al.	
	016	US-8329680-B2	12-11-2012	EVANS et al.	
	017	US-8436029-B2	05-07-2013	HICKEY et al.	
	018	US-8454945-B2	06-04-2013	McCOOK et al.	
	019	US-8466139-B2	06-18-2013	EVANS et al.	
	020	US-8822511-B2	09-02-2014	COMBS et al.	
	021	US-8993605-B2	03-31-2015	COMBS et al.	
	022	US-9073875-B2	07-07-2015	BOYALL et al.	
	023	US-9090640-B2	07-28-2015	BIERBACH et al.	
	024	US-9200045-B2	12-01-2015	LIU et al.	
	025	US-9220680-B2	12-29-2015	PERUMAL et al.	

Examiner Signature	/RAYMOND J HENLEY III/ (11/07/2023)	Date Considered	

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.J.H/

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 2 of 20

Complete if Known	
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Art Unit	Unassigned
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U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	026	US-9308181-B2	04-12-2016	KISAK et al.	
	027	US-9333190-B2	05-10-2016	AHMAD et al.	
	028	US-11261151-B2	03-01-2022	QUAY et al.	
	029	US-11572334	02-07-2023	QUAY; Steven C. et al.	
	030	US-20020025543-A1	02-28-2002	SERRERO; Ginette	
	031	US-20030021787-A1	01-30-2003	HUNG; David et al.	
	032	US-20030099694-A1	05-29-2003	CEVC; Gregor et al.	
	033	US-20040092894-A1	05-13-2004	HUNG; David et al.	
	034	US-20070059288-A1	03-15-2007	DINSMORE; Jonathan H. et al.	
	035	US-20070161063-A1	07-12-2007	LOVE; Susan et al.	
	036	US-20070190019-A1	08-16-2007	GUO; Chunfeng et al.	
	037	US-20080138391-A1	06-12-2008	CARRARA; Dario Norberto et al.	
	038	US-20080319092-A1	12-25-2008	SINGH; Jagat	
	039	US-20090068190-A1	03-12-2009	BORTZ; Jonathan David	
	040	US-20090098069-A1	04-16-2009	VACCA; Rita Downard	
	041	US-20090208944-A1	08-20-2009	GOETZ; Matthew P. et al.	
	042	US-20090281063-A1	11-12-2009	INAGI; Toshio et al.	
	043	US-20090291102-A1	11-26-2009	FORTIN; Samuel	
	044	US-20090291134-A1	11-26-2009	AHMAD; Ateeq et al.	

Examiner Signature	/RAYMOND J HENLEY III/ (11/07/2023)	Date Considered	

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(Use as many sheets as necessary)

Sheet 3 of 20

Complete if Known	
Application Number	18/128,536
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First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	045	US-20100015195-A1	01-21-2010	JAIN; Rajesh et al.	
	046	US-20100015200-A1	01-21-2010	McCLAIN; James B. et al.	
	047	US-20100069781-A1	03-18-2010	JOHANSEN; Jerald A. et al.	
	048	US-20100098659-A1	04-22-2010	WATSON; Richard L. et al.	
	049	US-20100112041-A1	05-06-2010	AHMAD; Ateeq et al.	
	050	US-20120010245-A1	01-12-2012	MASINI-ETEVE; Valerie	
	051	US-20120149761-A1	06-14-2012	QUAY; Steven C.	
	052	US-20120164075-A1	06-28-2012	AHMAD; Ateeq et al.	
	053	US-20120301541-A1	11-29-2012	HARONSKY; Elina et al.	
	054	US-20130046171-A1	02-21-2013	JOHANSEN; Jerald A. et al.	
	055	US-20130177590-A1	07-11-2013	COMBS; Andrew P. et al.	
	056	US-20130197087-A1	08-01-2013	SCHLOTZER; Ewald et al.	
	057	US-20140088059-A1	03-27-2014	PERUMAL; Omathanu P. et al.	
	058	US-20140193334-A1	07-10-2014	BIERBACH; Ulrich et al.	
	059	US-20140199391-A1	07-17-2014	BIRBARA; Philip J.	
	060	US-20150080339-A1	03-19-2015	WANG; Guangdi et al.	
	061	US-20150132388-A1	05-14-2015	ANGI; Erzsebet Reka et al.	

Examiner Signature	/RAYMOND J HENLEY III/ (11/07/2023)	Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 4 of 20

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	062	US-20150141391-A1	05-21-2015	CHINNAIYAN; Arul M. et al.	
	063	US-20150250802-A1	09-10-2015	LABRIE; Fernand et al.	
	064	US-20160346230-A1	12-01-2016	AHMAD; Ateeq et al.	
	065	US-20160375234-A1	12-29-2016	QUAY; Steven C.	
	066	US-20170145515-A1	05-25-2017	CHEN; Shu-Chih et al.	
	067	US-20170304232-A1	10-26-2017	KHAN; Seema Ahsan et al.	
	068	US-20180049999-A1	02-22-2018	QUAY; Steven C.	
	069	US-20180200206-A1	07-19-2018	QUAY; Steven C.	
	070	US-20190269697-A1	09-05-2019	LABRIE; Fernand	
	071	US-20200207704-A1	07-02-2020	QUAY; Steven C. et al.	

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Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]-Number[4]-Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	CN-101891635-A	11-24-2010	YANGTZE RIVER PHARMACEUTICAL GROUP., et al.		☒
	002	CN-102448467-A	05-09-2012	LITHERA INC.		☒
	003	CN-104203961-A	12-10-2014	XAVIER UNIVERSITY.		☒

Examiner Signature	/RAYMOND J HENLEY III/ (11/07/2023)	Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 5 of 20

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

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	004	CN-104230723-B	08-24-2016	ASYMCHEM LAB TIANJIN CO LTD.		☒
	005	CN-104352504-A	02-18-2015	ENDORECH INC.		☒
	006	CN-105579044-A	05-11-2016	DEL MAR PHARMACEUTICALS., et al.		☒
	007	EP-1709062-B9	02-13-2013	CEDARBURG PHARMACEUTICALS INC [US]		☐
	008	EP-2350111-A1	08-03-2011	SYNTHON BV [NL]		☐
	009	EP-3202420-A1	08-09-2017	BESINS HEALTHCARE LU SARL [LU]		☐
	010	EP-3202420-B1	03-04-2020	BESINS HEALTHCARE LU SARL [LU]		☐
	011	WO-0064416-A3	03-08-2001	LILLY CO ELI [US], et al.		☐
	012	WO-0174366-A1	10-11-2001	ASTRAZENECA AB [SE], et al.		☐
	013	WO-2008066783-A2	06-05-2008	ARIAD GENE THERAPEUTICS INC [US], et al.		☐
	014	WO-2008070463-A2	06-12-2008	JINA PHARMACEUTICALS INC [US], et al.		☐

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Sheet 6 of 20

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Attorney Docket Number	438558-758053

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	015	WO-2008070463-A9	09-18-2008	JINA PHARMACEUTICALS INC [US], et al.		☐
	016	WO-2009032699-A1	03-12-2009	DRUGTECH CORP [US], et al.		☐
	017	WO-2009069140-A1	06-04-2009	DABUR PHARMA LTD [IN], et al.		☐
	018	WO-2009120999-A2	10-01-2009	OLEMA PHARMACEUTICALS INC [US], et al.		☐
	019	WO-2009120999-A3	12-30-2009	OLEMA PHARMACEUTICALS INC [US], et al.		☐
	020	WO-2010066810-A1	06-17-2010	BESINS HEALTHCARE [BE], et al.		☐
	021	WO-2010135703-A2	11-25-2010	JINA PHARMACEUTICALS INC [US], et al.		☐
	022	WO-2011072244-A1	06-16-2011	SINAI SCHOOL MEDICINE [US], et al.		☐
	023	WO-2012050263-A1	04-19-2012	CJ CHEILJEDANG CORP [KR], et al.		☐
	024	WO-2013050280-A1	04-11-2013	COMMISSARIAT ENERGIE ATOMIQUE [FR]		☒
	025	WO-2013134230-A1	09-12-2013	XAVIER UNIVERSITY [US]		☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 7 of 20

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Application Number	18/128,536
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Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

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	026	WO-2014060640-A8	05-07-2015	FERMION OY [FI]		☐
	027	WO-2014134165-A1	09-04-2014	SLOAN KETTERING INST CANCER [US]		☐
	028	WO-2014141292-A2	09-18-2014	INTAS PHARMACEUTICALS LTD [IN]		☐
	029	WO-2015106094-A1	07-16-2015	ATOSSA GENETICS INC [US]		☐
	030	WO-2015138340-A1	09-17-2015	REPROS THERAPEUTICS INC [US]		☐
	031	WO-2015187727-A2	12-10-2015	ATOSSA GENETICS INC [US]		☐
	032	WO-2016168021-A1	10-20-2016	ATOSSA GENETICS INC [US]		☐
	033	WO-2017011623-A1	01-19-2017	ATOSSA GENETICS INC [US]		☐
	034	WO-2017070651-A1	04-27-2017	US HEALTH [US], et al.		☐
	035	WO-2017080770-A1	05-18-2017	ROBERT BOSCH GES FÜR MEDIZINISCHE FORSCHUNG MBH [DE]		☒
	036	WO-2019051368-A1	03-14-2019	ATOSSA GENETICS INC [US]		☐

Examiner Signature	/RAYMOND J HENLEY III/ (11/07/2023)	Date Considered	

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Sheet 8 of 20

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Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

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	037	WO-2019051370-A1	03-14-2019	ATOSSA GENETICS INC [US]		☐
	038	WO-2019051416-A1	03-14-2019	ATOSSA GENETICS INC [US]		☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 9 of 20

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

NON-PATENT LITERATURE DOCUMENTS

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	001	ACKERMAN A.B., et al., "Contrary View: The Breast is not an Organ Per Se, but a Distinctive Region of Skin and Subcutaneous Tissue," The American Journal of Dermatopathology, April 2007, Vol. 29 (2), pp. 211-218.	☐
	002	AHAMAD A., et al., "Endoxifen, A New Cornerstone of Breast Cancer Therapy: Demonstration of Safety, Tolerability and Systemic Bioavailability in Healthy Human Subjects," Clinical Pharmacology & Therapeutics, December 2010, Vol. 88 (6), pp. 814-817.	☐
	003	AHMAD A., et al., "Endoxifen, A New Treatment Option for Mania: A Double-Blind, Active-Controlled Trial Demonstrates the Antimanic Efficacy of Endoxifen," Clinical and Translational Science, Vol. 9 (5), October 2016, pp. 252-259.	☐
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	009	BATH, et al., "An Improved Sysnthesis of Raloxifene Hydrochoride: A Selective Estrogen Receptor Modulator," Heteroletters, Vol. 4 (4), 2014, pp. 515-518.	☐

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

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Sheet 10 of 20

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

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	010	BERNHARD H., et al., "Adoptive Transfer of Autologous, HER2-Specific, Cytotoxic T Lymphocytes for the Treatment of HER2-Overexpressing Breast Cancer," Cancer Immunology, Immunotherapy, 2008, Vol. 57, pp. 271-280.	☐
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	013	Clinical Trials Government, Identifier No. NCT01273168, "Endoxifen in Adults With Hormone Receptor Positive Solid Tumors," 10 January 2011, 10 pages.	☐
	014	Clinical Trials Government, Identifier No. NCT02311933, "Tamoxifen Citrate or Z-Endoxifen Hydrochloride in Treating Patients With Locally Advanced or Metastatic, Estrogen Receptor-Positive, HER2-Negative Breast Cancer," 9 December 2014, 13 pages.	☐
	015	DAVISON, et al., "In Vitro Effects on MCF-7 Breast Cancer Cells of Signal Transduction Inhibitor/Tamoxifen/ Eicosapentaenoic Acid Combinations and their Simultaneous Delivery Across Skin," Pharmaceutical Research, Vol. 25, 2008, pp.2516-2525.	☐
	016	DICKSCHEN K., et al., "Physiologically Based Pharmacokinetic Modeling of Tamoxifen and its Metabolites in Women of Different CYP2D6 Phenotypes Provides New Insight into the Tamoxifen Mass Balance," Frontiers in Pharmacology, Vol.3 (92), May 2012, 15 pages, www.frontiersin.org.	☐
	017	DONNEYONG M.M., et al., "Risk of Mortality with Concomitant use of Tamoxifen and Selective Serotonin Reuptake Inhibitors: Multi-Database Cohort Study," BMJ, 30 September 2016, Vol. 354 (i5014), 20 pages.	☐
	018	Dowsett et al., The effect of anastrozole on the pharmacokinetics of tamoxifen in post-menopausal women with early breast cancer. British J Cancer 1999; 79(2), 311-315.	☐

Examiner Signature	/RAYMOND J HENLEY III/ (11/07/2023)	Date Considered	

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Substitute for form 1449/PTO	Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)	Application Number	18/128,536
	Filing Date	03-30-2023
	First Named Inventor	QUAY; Steven C.
	Art Unit	Unassigned
	Examiner Name	Unassigned
Sheet 11 of 20	Attorney Docket Number	438558-758053

NON-PATENT LITERATURE DOCUMENTS			
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	019	Extended European Search Report for EP Application EP17857260.8, dated 24 March 2020, 16 pages.	☐
	020	Extended European Search Report for European Application No. EP18853361.6, dated May 28, 2021, 5 pages.	☐
	021	FASCHING P.A., et al., "Ki67, Chemotherapy Response and Prognosis in Breast Cancer Patients receiving Neoadjuvant Treatment," BMC Cancer, Vol. 11, Article 486, 2011, 13 pages.	☐
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	025	GALEANA P.C., et al., "Ki67 Changes Identify Worse Outcomes in Residual Breast Cancer Tumors After Neoadjuvant Chemotherapy," The Oncologist, Vol. 23 (6), June 2018, pp. 670-678.	☐
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Sheet 12 of 20

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	028	GOETZ M.P., et al., "A First-in-Human Phase I Study of the Tamoxifen (TAM) Metabolite, Z-Endoxifen Hydrochloride (Z-Endx) in Women with Aromatase Inhibitor (AI) Refractory Metastatic Breast Cancer (MBC) (NCT01327781)," San Antonio Breast Conference, December 2013, PD3-4, 4 pages.	☐
	029	GOETZ M.P., et al., "Abstract PD2-03: Final Results of a First-in-Human Phase I Study of the Tamoxifen (TAM) Metabolite, Z-Endoxifen Hydrochloride (Z-Endx) in Women with Aromatase Inhibitor (AI) Refractory Metastatic Breast Cancer (MBC) (NCT01327781)," San Antonio breast cancer symposium, 8-12 December 2015, 5 pages.	☐
	030	GOETZ M.P., et al., "Final Results of a First in Human Phase I Study of the Tamoxifen (TAM) Metabolite, Endoxifen Hydrochloride in Women with Aromatase Inhibitor (AI) Refractory Metastatic Breast Cancer (MBC) (NCT01327781)," San Antonio Breast Conference, 2015, PD203, 1 page.	☐
	031	GOETZ M.P., et al., "First-in-Human Phase I Study of the Tamoxifen Metabolite Z-Endoxifen in Women With Endocrine-Refractory Metastatic Breast Cancer," DOI: https://ascopubs.org/doi/10.1200/JCO.2017.73.3246 , Vol. 35, No. 30, October 20, 2017, 16 pages.	☐
	032	HAWSE J.R., et al., "Endoxifen's Molecular Mechanisms of Action are Concentration Dependent and Different than that of other Anti-Estrogens," PLOS one, Vol. 8 (1), Januray 2013, e54613, 18 pages.	☐
	033	HENDERSON S.L., et al., "Profound Reduction in Tamoxifen Active Metabolite Endoxifen in a Breast Cancer Patient Treated with Rifampin Prior to Initiation of an Anti-TNF a Biologic for Ulcerative Colitis: a Case Report," BMC cancer, Vol. 16 (304), 11 May 2016, 6 pages.	☐
	034	HERSHMAN, et al., "Early Discontinuation and Non-adherence to Adjuvant Hormonal Therapy in a Cohort of 8, 769 early Stage Breast Cancer Patients," Journal of Clinical Oncology, Vol. 26(27), 20 September 2010.	☐

Examiner Signature	/RAYMOND J HENLEY III/ (11/07/2023)	Date Considered	

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 13 of 20

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	Unassigned
Examiner Name	Unassigned
Attorney Docket Number	438558-758053

NON-PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	035	IKEDA H., et al., "Combination Treatment with Fulvestrant and various Cytotoxic Agents (Doxorubicin, Paclitaxel, Docetaxel, Vinorelbine, and 5-Fluorouracil) has a Synergistic Effect in Estrogen Receptor-Positive Breast Cancer," Cancer Science, Vol. 102 (11), November 2011, pp. 2038-2042, 5 Pages.	☐
	036	INGLE, et al., "Variation in Anastrozole Metabolism and Pharmacodynamics in Women with Early Breast Cancer," Cancer Research, Vol. 70 (8), 15 April 2010, pp. 3278-3286.	☐
	037	International Preliminary Report on Patentability for the application no. PCT/US2020/040757, mailed 13 January 2022, 9 pages.	☐
	038	International Report on Patentability for International Application no. PCT/US2018/050193, mailed March 26, 2020, 7 pages.	☐
	039	International Search Report and Written Opinion for International Application no. PCT/US2018/050193, mailed January 04, 2019, 9 pages.	☐
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	041	JANSEN, et al., "High miR-26a and Low CDC2 Levels Associate with Decreased EZH2 Expression and with Favorable Putcome on Tamoxifen in Metastatic Breast Cancer," Breast Cancer ResearchTreatment, Vol. 133, 2012, pp. 937-947.	☐
	042	JOHNSON M.D., et al., "Pharmacological Characterization of 4-Hydroxy-N-Desmethyl Tamoxifen, A Novel Active Metabolite of Tamoxifen," Breast Cancer Research and Treatment, Vol. 85, 2004, pp. 151-159.	☐
	043	JOHNSON R.E., et al., "Gynecomastia - Evaluation and Current Treatment Options," Therapeutics and Clinical Risk Management, Vol. 7, 2011, pp. 145-148.	☐
	044	JORDAN, C. New insights into the metabolism of tamoxifen and its role in the treatment and prevention of breast cancer. Steroids. 2007 Nov; 72(13): 829-842.	☐

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Sheet 14 of 20

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	045	Journal of Pharmaceutical Science and Technology, Japan, 2006, Vol. 66, No. 6, pp. 435-439. (No English Translation available. Document showing a well-known technique).	☐
	046	KAMDEM, et al., "In Vitro and in Vivo Oxidative Metabolism and Glucuronidation of Anastrozole," British Journal of Clinical Pharmacology, Vol. 70 (6), 2010, pp. 854-869.	☐
	047	KARLSSON H., et al., "CAR T-Cell Therapy: The Role of Physical Barriers and Immunosuppression in Lymphoma," Gene Ther, August 2015, Vol. 26(8), https://pubmed.ncbi.nlm.nih.gov/26230974/ , pp: 498-505.	☐
	048	KAUR, et al., "Design, Synthesis and Evaluation of Ospemifene Analogs as Anti-Breast Cancer Agents," European Journal of Medicinal Chemistry, Vol. 86, 30 October 2014, pp. 211-218.	☐
	049	KEBAMO, et al., The Role of biotransformation in drug discovery and development. J Drug Metab. Toxicol. 2015; 6(5): 1-13.	☐
	050	LANCET, "Aromatase Inhibitors Versus Tamoxifen in Early Breast Cancer: Patient-Level Meta-Analysis of the Randomised Trials," Vol. 386, 2015, pp. 1341-1352.	☐
	051	LARI, et al., "Biological Markers in DCIS and Risk of Breast Recurrence: A Systematic Review," Journal of Cancer, Vol. 2, 2011, pp. 232- 261.	☐
	052	LAZZERONI M., et al., "Oral Low Dose and Topical Tamoxifen for Breast Cancer Prevention: Modern Approaches for an Old Drug," Breast Cancer Research, Vol. 14(214), 2012, 11 pages.	☐
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	055	LEHMANN, "Identification of Human Triple-Negative Breast Cancer Subtypes and Preclinical Models for Selection of Targeted Therapies," Journal of Clinical Invest, Vol. 121 (7), 2011, pp.2750-2767.	☐
	056	LEMAINE, et al., "Gynecomastia in Adolescent Males," Seminars Plastic Surgery, Vol. 27 (1), Febraury 2013, pp. 56-61.	☐
	057	LI L., et al., "Prognostic Values of Ki-67 in Neoadjuvant Setting for Breast Cancer: A Systematic Review and Meta-Analysis," Future Oncology, Vol. 13(11), May 2017, pp. 1021-1034.	☐
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	059	LOVE, et al., "A Feasibility Study of the Intraductal Administration of Chemotherapy," Cancer Prevention Research, Vol. 1, 2012, pp. 51-58.	☐
	060	MAH, et al., "A Miniaturized Flow-through Cell to Evaluate Skin Permeation of Endoxifen," International Journal of pharmaceutics, Vol. 441, 2013, pp. 433-440.	☐
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	062	MANNI ET AL: "Combination of Antiestrogens and Omega-3 Fatty Acids for Breast Cancer Prevention", BIOMED RESEARCH INTERNATIONAL, vol. 2015, 1 January 2015 (2015-01-01), pages 1-10, XP055561178, ISSN: 2314-6133, DOI: 10.1155/2015/638645.	☐
	063	MANSEL R., et al., "A Phase II Trial of Afimoxifene (4-hydroxyTamoxifen gel) for Cyclical Mastalgia in Premenopausal Women," Breast Cancer Research Treatment, December 2007, Vol. 106 (3), pp. 389-397.	☐

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	064	MAXIMOV P.Y., et al., "Structure-Function Relationships of Estrogenic Triphenylethylenes Related to Endoxifen and 4- Hydroxytamoxifen," Journal of Medicinal Chemistry, 22 April 2010, Vol. 53 (8), pp. 3273-3283.	☐
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	067	MILLER, et al., "Stereospecific Synthesis of (Z)-Tamoxifen via Carbometallation of Alkynylsilanes," The Journal of Organic Chemistry, Vol. 50 (12), 1985, pp. 2121-2123.	☐
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	069	OKEN M.M., et al., "Toxicity and Response Criteria of the Eastern Cooperative Oncology Group," American Journal of Clinical Oncology, December 1982, Vol. 5(6), pp. 649-655.	☐
	070	PARTRIDGE, et al., "Adherence to Initial Adjuvant Anastrozole Therapy among Women with Early Stage Breast Cancer," Journal Clinical Oncology, 01 Febuary 2008, Vol. 26 (4).	☐
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	072	ROBERTSON, et al., "Fulvestrant: Pharmacokinetics and Pharmacology," British Journal of Cancer, 2004, Vol. 90, pp. S7-S10.	☐
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	074	ROUANET P., et al., "Neoadjuvant Percutaneous 4-Hydroxytamoxifen Decreases Breast Tumoral Cell Proliferation: A Prospective Controlled Randomized Study Comparing Three Doses of 4-hydroxytamoxifen Gel to Oral Tamoxifen," Journal of Clinical Oncology, 1 May 2005, Vol. 23(13), pp. 2980-2987.	☐
	075	SANO, et al., "Short-step Synthesis of Droloxifene via the Three-Component Coupling Reaction among Aromatic Aldehyde, Cinnamyltrimethylsilane, and 13-Chlorophenetole," Tetrahedron Letters, 6 March 2006, Vol. 47 (10), pp. 1631-1635.	☐
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	077	SOLTAMOX Oral Solution, Rx Only, Savient Pharmaceuticals, Inc, 25 August 2005, 37 pages.	☐
	078	STEARNS, et al., "Preclinical and Clinical Evaluation of Intraductally Administered Agents in Early Breast Cancer," Science Translational Medicine, Oct. 26, 2011, Vol. 3 (106), 19 pages, 106ra108.	☐
	079	SUN M., et al., "Construction and Evaluation of a Novel Humanized HER2-Specific Chimeric Receptor," Breast Cancer Research, 2014, Vol. 16:R61, 10 pages.	☐
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	081	UMAREDDY, et al., "Improved Process for Centchroman, A Selective Estrogen Receptor Modulator (SERM)," Journal of Chemical and Pharmaceutical Research, 2015, Vol. 7 (7), pp. 736-741.	☐
	082	UMAREDDY, et al., "Total Synthesis of Lasofoxifene and Nafoxidine," An International Journal for Rapid Communication of Synthetic Organic Chemistry, 2016, Vol. 46 (4), pp. 309-313.	☐
	083	VERGOTE, et al., "Fulvestrant is an Effective and Well-Tolerated Endocrine Therapy for Postmenopausal Women with Advanced Breast Cancer," Results from Clinical Trials, British Journal of Cancer, 90 (Suppl), 2004, pp. S11-S14.	☐

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	First Named Inventor	QUAY; Steven C.
	Art Unit	Unassigned
	Examiner Name	Unassigned
Sheet 18 of 20	Attorney Docket Number	438558-758053

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	084	WELSH, J., "Induction of apoptosis in breast cancer cells in response to vitamin D and antiestrogens", BIOCHEMISTRY AND CELL BIOLOGY, vol. 72, no. 11-12, 1994, pages 537-545, XP009511548, ISSN: 0829-8211.	☐
	085	WU, et al., "Single Cell MicroRNA Analysis using Microftuidic Ftow Cytometry," PLOS One, 2013, Vol. 8 (1), e55044.	☐
	086	WU X., et al., "The Tamoxifen Metabolite, Endoxifen, is a Potent Antiestrogen that Targets Estrogen Receptor Alpha for Degradation in Breast Cancer Cells," Cancer Research, 01 March 2009, Vol. 69(5), , pp. 1722-1727.	☐
	087	YAN YAODONG., "Design and Development of Sustained-Release and Controlled-Release Formulations," Chinese Medicine Science and Technology Publishing House, 30 June 2006 (2006-06-30), pp. 421-428.	☐
	088	YANG Y., et al., "Dendron-Based Micelles for Topical Delivery of Endoxifen: A Potential Chemo-Preventive Medicine for Breast Cancer," Advanced Functional Materials, 2014, Vol. 24, pp. 2442-2449.	☐
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	092	ZHAO Y., et al., "A Herceptin-Based Chimeric Antigen Receptor with Modified Signaling Domains Leads to Enhanced Survival of Transduced T Lymphocytes and Antitumor Activity," The Journal of Immunology, https://www.researchgate.net/publication/38024914 , November, 2009, Vol. 183(9), pp: 5563-5574.	☐

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Sheet	20	of	20	Attorney Docket Number	438558-758053

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Erin M. Gaffney/	Date (YYYY-MM-DD)	2023-08-04
Name/Print	Erin M. Gaffney, Ph.D.	Registration Number	81,479

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/128,536	03/30/2023	Steven C. Quay	438558-758053	1025

187495 7590 11/14/2023

DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

EXAMINER	
HENLEY III, RAYMOND J	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
11/14/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

seattlepatentdocket@us.dlapiper.com

Decision Dismissing Petition under 37 CFR 1.138(c)	Application No. 18/128,536	Applicant(s) Quay et al.

The declaration of express abandonment will not be recognized

This is in response to the petition under 37 CFR 1.138(c), for express abandonment to avoid publication of the above-identified application.

The petition is **DISMISSED**.

The express abandonment will **not** be recognized for the reason(s) indicated below:

- ☑ The petition under 37 CFR 1.138(c) was not filed in sufficient time to permit the appropriate officials to recognize the abandonment and remove the application from the publication process.
- ☐ The petition was not signed by a party authorized under 37 CFR 1.138(b).
- ☐ The Application was published in compliance with 35 U.S.C. 122(b), and it is available on the USPTO web site.
- ☐ Petition fee was not paid.
- ☐ The application has not been assigned an official filing date. A request for reconsideration of the petition for express abandonment may be submitted once the application is accorded an official filing date. If the initial request for express abandonment was filed before the application was processed, but the application as initially submitted was accorded a filing date, then no fee is due with any request for reconsideration. If the application as deposited was not accorded a filing date, then any request for consideration must include the fee indicated in 37 CFR 1.138.

The application **has/will be published** as scheduled.

Telephone inquiries may be directed to the Application Assistance Unit at 1-888-786-0101 or 571-272-4200.

/HAIMANOT A CHRISTIAN/
Office of Data Management
Patent Publication Branch

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DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

EXAMINER	
HENLEY III, RAYMOND J	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
11/14/2023	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

seattlepatentdocket@us.dlapiper.com

Office Action Summary	Application No. 18/128,536	Applicant(s) Quay et al.	
	Examiner RAYMOND J HENLEY III	Art Unit 1629	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on all dates up to the date of this Office action.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 158-201 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 158-201 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☑ The drawing(s) filed on March 30, 2023 is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date August 04, 2023.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

CLAIMS 158-201 ARE PRESENTED FOR EXAMINATION

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

Applicant's Preliminary Amendment and Information Disclosure Statements filed August 04, 2023 have been received and entered into the application. Accordingly, the application papers have been amended as per Applicant's direction. Also, as reflected by the attached, completed copies of form PTO/SB/08, the cited references have been considered by the Examiner.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP § 2146 *et seq.* for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The filing of a terminal disclaimer by itself is not a complete reply to a nonstatutory double patenting (NSDP) rejection. A complete reply requires that the terminal disclaimer be accompanied by a reply requesting reconsideration of the prior Office action. Even where the NSDP rejection is provisional the reply must be complete. See MPEP § 804, subsection I.B.1. For a reply to a non-final Office action, see 37 CFR 1.111(a). For a reply to final Office action, see 37 CFR 1.113(c). A request for reconsideration while not provided for in 37 CFR 1.113(c) may be filed after final for consideration. See MPEP §§ 706.07(e) and 714.13.

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The actual filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/apply/applying-online/eterminal-disclaimer.

Claims 158-201 are rejected on the ground of nonstatutory double patenting as being unpatentable over (a) claims 1-22 of U.S. Patent No. 11,680,036 or (b) claims 1-22 of U.S. Patent No. 11,572,334, (each cited by Applicant). Although the claims at issue are not identical, they are not patentably distinct from each other because the present claims provide broadly for an "enteric material", (e.g., at least claim 1), while the patented claims are directed to specific types of enteric formulations, i.e., a suspension or a capsule, thus making the presently claimed subject matter obvious to one of ordinary skill in the art.

None of the claims are currently in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RAYMOND J HENLEY III whose telephone number is (571)272-0575. The examiner can normally be reached M-F 6-2:30pm EST.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey S Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of published or unpublished applications may be obtained from Patent Center. Unpublished application information in Patent Center is available to registered users. To file and manage patent submissions in Patent Center, visit: https://patentcenter.uspto.gov. Visit https://www.uspto.gov/patents/apply/patent-center for more information about Patent Center and https://www.uspto.gov/patents/docx for information about

filing in DOCX format. For additional questions, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/RAYMOND J HENLEY III/
Primary Examiner, Art Unit 1629
November 07, 2023

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/128,536	03/30/2023	Steven C. Quay	438558-758053

CONFIRMATION NO. 1025

187495
DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

PUBLICATION NOTICE

OC000000064634363

Date Mailed: 11/16/2023

Title:METHODS FOR MAKING AND USING ENDOXIFEN

Publication No.US-2023-0365490-A1
Publication Date:11/16/2023

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently http://www.uspto.gov/patft/.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently https://portal.uspto.gov/pair/PublicPair. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Managment, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/128,536	04/15/2024 08:36:04 PM Z ET	438558-758053

Title of Invention

METHODS FOR MAKING AND USING ENDOXIFEN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1025	FILED BY	Christina Campbell
PATENT CENTER #	65100460	AUTHORIZED BY	Erin Gaffney
CUSTOMER #	187495	FILING DATE	03/30/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Steven C. Quay

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 071896	E20244EK48466217	Erin Gaffney

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	1	170.00
			TOTAL AMOUNT:	$170.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION OVER A PRIOR PATENT

APPLICATION #	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET #
18128536	03/30/2023	Steven Quay	438558-758053

Title of Invention

METHODS FOR MAKING AND USING ENDOXIFEN

☑ Filing of terminal disclaimer does not obviate requirement for response under 37 CFR 1.111 to outstanding Office Action

☑ This electronic Terminal Disclaimer is not being used for a Joint Research Agreement.

Owner	Percent Interest
Atossa Therapeutics, Inc.	100%
Total	100%

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of any patent granted on pending reference Application Number(s)

Application #	Filing Date

as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the reference application are commonly owned. This agreement runs with any patent granted on the

instant application and is binding upon the grantee, its successors or assigns.
In making the above disclaimer, the owner does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, "as the term of any patent granted on said reference application may be shortened by any terminal disclaimer filed prior to the grant of any patent on the pending reference application," in the event that any such patent granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321, has all claims canceled by a reexamination certificate, is reissued, or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.

The owner(s) of percent interest listed above in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of prior patent number(s)

Patent #
11680036
11572334

as the term of said prior patent is presently shortened by any terminal disclaimer. The owner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the prior patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.
In making the above disclaimer, the owner does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the prior patent, "as the term of said prior patent is presently shortened by any terminal disclaimer," in the event that said prior patent later:
- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.



Terminal disclaimer fee under 37 CFR 1.20(d) included with Electronic Terminal Disclaimer request.

Applicant claims the following entity status:
Small

I hereby declare that all statements made herein of my own knowledge are true and that all statemnts made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I certify, in accordance with 37 CFR 1.4(d)(4) that I am: An attorney or agent registered to practice before the Patent and Trademark Office who is of record in this application

Signature	Name	Registration #
/Erin M. Gaffney/	Erin Gaffney	81479

* Statement under 37 CFR 3.73(b) is required if terminal disclaimer is signed by the assignee (owner). Form PTO/SB/96 may be used for making this certification. See MPEP 324.

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APPROVAL LETTER

APPLICATION #	FILING DATE	APPLICANT/PATENT UNDER REEXAMINATION
18/128,536	03/30/2023	Steven Quay

Title of Invention

METHODS FOR MAKING AND USING ENDOXIFEN

Electronic terminal disclaimer filed on 04/15/2024

☑ Approved

This patent is subject to a Terminal Disclaimer

Approved / Disapproved by: Electronic Terminal Disclaimer automatically approved

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/128,536	**04/15/2024 08:36:04 PM Z ET**	**438558-758053**

Title of Invention

METHODS FOR MAKING AND USING ENDOXIFEN

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CUSTOMER #	187495	FIRST NAMED INVENTOR	Steven C. Quay
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Erin Gaffney

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
petition-request.pdf	3	Terminal Disclaimer-Filed (Electronic)	49 KB
grantLetter.pdf	1	Terminal Disclaimer-Electronic-Approved	19 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
petition-request.pdf	834F1908D38ED58901F4877FB7F9712B0DA12E636B08D61327D43984C4763113F21C2EA5A6C9F7CC968E9DBF6B386B1C3E

	E20E07F93341729F54D9DCC564224B
grantLetter.pdf	4F9C37DB35DB56F56E3ACCCF0D3B370D37DD077391D6D8BF E9B53BC2530213D599BCDFA361E3FA873793879E588658F808 9797ED0E3619EF05A8EFF022CE0E23

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on April 15, 2024.

DLA PIPER LLP (US)

By: /Christina Campbell/

Attorney Docket No.: 438558-758053

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Confirmation No. 1025
Steven C. Quay et al.	
Application No.: 18/128,536	Examiner: RAYMOND J HENLEY III
Filed: March 30, 2023	Art Unit: 1629
For: METHODS FOR MAKING AND USING ENDOXIFEN	AMENDMENT
Customer No. 187495	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Non-Final Office Action mailed November 14, 2023, please enter the following amendments and remarks. An Information Disclosure Statement and Terminal Disclaimer also accompany this response.

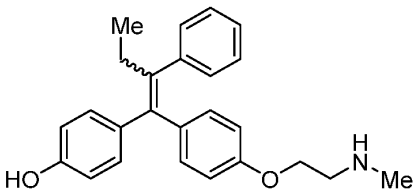
Remarks begin on page 8.

Listing of Claims:

157. (Canceled)

158. (Previously Presented) A composition comprising an endoxifen and an enteric material, wherein:

the endoxifen comprises a compound of Formula (III):



Formula (III)

or a pharmaceutically acceptable salt thereof; and

at least 90% by weight of the compound of Formula (III) is (*Z*)-endoxifen.

159. (Previously Presented) The composition of claim 158, wherein the pharmaceutically acceptable salt is selected from the group consisting of an: arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, Teoclate, triethiodide, benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc salt.

160. (Previously Presented) The composition of claim 158, wherein the pharmaceutically acceptable salt of the compound of Formula (III) is endoxifen gluconate.

161. (Previously Presented) The composition of claim 158, wherein the composition is a delayed-release formulation.

162. (Previously Presented) The composition of claim 158, wherein the composition is a tablet.

163. (Previously Presented) The composition of claim 158, wherein the composition is a capsule.

164. (Previously Presented) The composition of claim 158, wherein the composition is uncoated.

165. (Previously Presented) The composition of claim 158, wherein the composition comprises an enteric coating.

166. (Previously Presented) The composition of claim 158, wherein the composition is formulated as a suspension.

167. (Previously Presented) The composition of claim 166, wherein the suspension comprises a syrup or an elixir.

168. (Previously Presented) The composition of claim 166, wherein the suspension comprises a fluid.

169. (Previously Presented) The composition of claim 168, wherein the fluid comprises an alcohol.

170. (Previously Presented) The composition of claim 169, wherein the alcohol comprises ethanol.

171. (Previously Presented) The composition of claim 166, wherein the suspension comprises an alcohol, a plant oil, a mineral oil, a glycol, an agar, or a mixture thereof.

172. (Previously Presented) The composition of claim 166, wherein the suspension comprises ethanol, mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, vegetable oil, stearic acid, sodium lauryl sulfate, or a mixture thereof.

173. (Previously Presented) The composition of claim 158, wherein the compound of Formula (III) is stable in the composition for at least 10 days at about 25°C.

174. (Previously Presented) The composition of claim 158, formulated such that the composition is resistant to dissolution in an acidic environment for at least 2 hours, as measured in a dissolution test performed according to a method of USP 711.

175. (Previously Presented) The composition of claim 158, formulated such that the composition releases no more than 10% of the (*Z*)-endoxifen over 2 hours in gastric fluid, as measured in a dissolution test performed according to a method of USP 711.

176. (Previously Presented) The composition of claim 158, formulated such that the composition releases at least 50% of the (*Z*)-endoxifen within 8 hours in intestinal fluid, as measured in a dissolution test performed according to a method of USP 711.

177. (Previously Presented) The composition of claim 158, wherein the composition further comprises hydroxypropylmethyl cellulose.

178. (Previously Presented) The composition of claim 158, wherein the composition further comprises a filler.

179. (Previously Presented) The composition of claim 178, wherein the filler comprises a sugar, salt, talc, calcium carbonate, microcrystalline cellulose, methyl cellulose, carboxymethyl cellulose, kaolin, mannitol, silicic acid, sorbitol, starch, pregelatinized starch, or combinations thereof.

180. (Previously Presented) The composition of claim 158, wherein the composition further comprises a disintegrant.

181. (Previously Presented) The composition of claim 158, wherein the composition further comprises a lubricant.

182. (Previously Presented) The composition of claim 181, wherein the lubricant comprises calcium stearate, magnesium stearate, zinc stearate, mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil, ethyl oleate, ethyl laureate, agar, or combinations thereof.

183. (Previously Presented) The composition of claim 158, wherein the composition comprises from 0.01 mg to 200 mg (*Z*)-endoxifen.

184. (Previously Presented) The composition of claim 158, wherein the composition comprises from 1 mg to 20 mg of (*Z*)-endoxifen.

185. (Previously Presented) The composition of claim 158, wherein the composition comprises from 1 mg to 4 mg of (*Z*)-endoxifen.

186. (Previously Presented) The composition of claim 158, wherein the composition comprises 8 mg of (*Z*)-endoxifen.

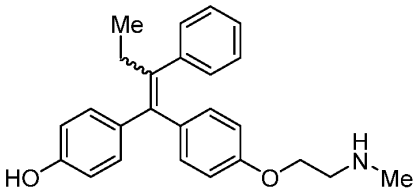
187. (Previously Presented) A method of making the composition of claim 166, the method comprising suspending the endoxifen and the enteric material in a fluid.

188. (Previously Presented) The method of claim 187, wherein the fluid comprises an alcohol, ethanol, a plant oil, a mineral oil, a glycol, an agar, glycerin, sorbitol, mannitol, polyethylene glycol, vegetable oil, stearic acid, sodium lauryl sulfate, or a mixture thereof.

189. (Previously Presented) A method comprising administering to a subject a composition comprising an endoxifen and an enteric material,

wherein:

the endoxifen comprises a compound of Formula (III):



Formula (III)

or a pharmaceutically acceptable salt thereof; and

at least 90% by weight of the compound of Formula (III) is (*Z*)-endoxifen.

190. (Previously Presented) The method of claim 189, comprising administering 1 mg to 20 mg of (*Z*)-endoxifen.

191. (Previously Presented) The method of claim 189, comprising administering 1 mg to 4 mg of (*Z*)-endoxifen.

192. (Previously Presented) The method of claim 189, comprising administering 8 mg of (*Z*)-endoxifen.

193. (Previously Presented) The method of claim 189, wherein the administering of the composition maintains the subject's plasma endoxifen at a steady state level above 30 nM.

194. (Previously Presented) The method of claim 189, wherein the administering of the composition maintains the subject's plasma endoxifen at a steady state level from 30 nM to 300 nM.

195. (Previously Presented) The method of claim 189, further comprising releasing no more than 10% of the (*Z*)-endoxifen in a stomach of the subject within 2 hours following the administrating of the composition.

196. (Previously Presented) The method of claim 189, further comprising releasing at least 50% of the (*Z*)-endoxifen in a small intestine of the subject within 8 hours following the administrating of the composition.

197. (Previously Presented) The method of claim 189, further comprising producing an area under curve ($AUC_{0\text{-}inf}$) of (*Z*)-endoxifen in the subject of from 200 hr*ng/mL to 10,000 hr*ng/mL per 4 mg of (*Z*)-endoxifen administered.

198. (Previously Presented) The method of claim 189, further comprising producing a maximum blood plasma concentration (C_{max}) of (*Z*)-endoxifen in the subject of from 14 ng/mL to 62 ng/mL per 4 mg of (*Z*)-endoxifen administered.

199. (Previously Presented) The method of claim 189, further comprising treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in the subject in need thereof.

200. (Previously Presented) The method of claim 199, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, ductal carcinoma *in situ*, lobular carcinoma *in situ*, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

201. (Previously Presented) The method of claim 199, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is tamoxifen-refractory or tamoxifen resistant.

REMARKS

Upon entry of this amendment, claims 158-201 will be pending in the present application. Applicants reserve the right to pursue any canceled subject matter in a related, future application. Support for the amendments can be found in the specification as originally filed. Accordingly, no new matter has been added. Reconsideration is respectfully requested.

Double Patenting

Claims 158-201 were rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over (a) claims 1-22 of U.S. Patent No. 11,680,036 or (b) claims 1-22 of U.S. Patent No. 11,572,334.

The enclosed terminal disclaimer overcomes the double patenting rejection and, accordingly, claims 158-201 should be allowed. The Applicant does not concede the merits of this rejection, and accordingly files this terminal disclaimer to expedite allowance of the pending claims without expressly or impliedly admitting that the pending claims are in fact unpatentable over the claims of (a) claims 1-22 of U.S. Patent No. 11,680,036 or (b) claims 1-22 of U.S. Patent No. 11,572,334.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Further, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 07-1896.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-839-4805.

Respectfully submitted,

Dated: April 15, 2024

/Erin M. Gaffney/

Erin M. Gaffney, Ph.D.
Registration No. 81,479

DLA PIPER LLP (US)
701 Fifth Avenue, Suite 6900
Seattle, Washington 98104-7029
Tel: (206) 839-4800
Fax (206) 839-4801

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Inventor:	Steven C. Quay et al.	Group Art Unit:	1629
Serial Number:	18/128,536	Examiner:	RAYMOND J HENLEY III
Filing or 371 (c) Date:	March 30, 2023	**CONFIRMATION NO:**	**1025**
Title:	METHODS FOR MAKING AND USING ENDOXIFEN	CUST. NO.:	187495

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

INFORMATION DISCLOSURE STATEMENT UNDER 37 CFR § 1.97

Commissioner for Patents:

An Information Disclosure Statement along with attached PTO/SB/08 is hereby submitted. A copy of each listed publication is submitted, if required, pursuant to 37 CFR §§1.97-1.98, as indicated below.

The Examiner is requested to review the information provided and to make the information of record in the above-identified application. The Examiner is further requested to initial and return the attached PTO/SB/08 in accordance with MPEP § 609.

The right to establish the patentability of the claimed invention over any of the information provided herewith, and/or to prove that this information may not be prior art, and/or to prove that this information may not be enabling for the teachings purportedly offered, is hereby reserved.

This statement is not intended to represent that a search has been made or that the information cited in the statement is, or is considered to be, prior art or material to patentability as defined in § 1.56.

The subject matter of this application is also related to that of U.S. Application No. 17/580,428 which is now issued Patent No. 11,572,334, issued on February 7, 2023 (hereinafter, "'334 patent"). The present application is a continuation of the '334 patent. The '334 patent is the subject of a Post Grant Review (PGR) between its assignee, Atossa Therapeutics, Inc., and Intas Pharmaceuticals Ltd. The PGR was filed on August 18, 2023, and has been assigned Case No. PGR2023-00043.

A. ☐ *37 CFR § 1.97 (b).* This Information Disclosure Statement should be considered by the Office because:

☐ (1) It is being filed within 3 months of the filing date of a national application and is other than a continued prosecution application under § 1.53 (d);

-- OR --

☐ (2) It is being filed within 3 months of entry of the national stage as set forth in § 1.491 in an international application;

-- OR --

☐ (3) It is being filed before the mailing of a first Office action on the merits;

-- OR --

☐ (4) It is being filed before the mailing of a first Office action after the filing of a request for continued examination under § 1.114.

B. ☒ *37 CFR § 1.97(c).* Although this Information Disclosure Statement is being filed after the period specified in *37 CFR § 1.97(b),* above, it is filed before the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application such as an Ex Parte Quayle, this Information Disclosure Statement should be considered because it is accompanied by one of:

☐ a statement as specified in §1.97 (e) provided concurrently herewith;

-- OR --

☒ a fee of $104.00 as set forth in § 1.17 (p) authorized below, enclosed, or included with the payment of other papers filed together with this statement.

C. ☐ *37 CFR § 1.97 (d).* Although this Information Disclosure Statement is being filed after the mailing date of the earlier of (1) a final office action under § 1.113, (2) a notice of allowance under § 1.311, or (3) an action that otherwise closes prosecution in the application, it is being filed before payment of the issue fee and should be considered because it is accompanied by:

i. a statement as specified in § 1.97 (e);

-- AND --

ii. a fee of $260.00 as set forth in §1.17(p) is authorized below, enclosed, or included with the payment of other papers filed together with this Statement.

D. ☐ *37 CFR §1.97 (e).* Statement.

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (c);

-- AND/OR --

☐ A statement is provided herewith to satisfy the requirement under 37 CFR §§ 1.97 (d);

-- AND/OR --

☐ A copy of a dated communication from a foreign patent office clearly showing that the information disclosure statement is being submitted within 3 months of the filing date on the communication is provided in lieu of a statement under 37 C.F.R. § 1.97(e) (1) as provided for under MPEP 609.04(b) V.

E. ☐ *Statement Under 37 C.F.R. §1.704(d).* Each item of information contained in the information disclosure statement was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office or is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office that was received by an individual designated in § 1.56(c) not more than thirty (30) days prior to the filing of this information disclosure statement. This statement is made pursuant to the requirements of 37 C.F.R. §1.704(d) to avoid reduction of the period of adjustment of the patent term for Applicant(s) delay.

F. ☒ *37 CFR §1.98 (a) (2).* The content of the Information Disclosure Statement is as follows:

☐ Copies of each of the references listed on the attached Form PTO/SB/08 are enclosed herewith.

-- OR --

☒ Copies of U.S. Patent Documents (issued patents and patent publications) listed on the attached Form PTO/SB/08 are not enclosed.

-- AND/OR --

☒ Copies of Foreign Patent Documents and/or Non Patent Literature Documents listed on the attached Form PTO/SB/08 are enclosed in accordance with 37 CFR §1.98 (a)(2).

-- AND/OR --

☐ Copies of pending unpublished U.S. patent applications are enclosed in accordance with 37 CFR §1.98 (a) (2) (iii).

G. ☐ *37 CFR §1.98(a)(3).* The Information Disclosure Statement includes non-English patents and/or references.

☐ Pursuant to 37 CFR §1.98(a)(3)(i), a concise explanation of the relevance of each patent, publication or other information provided that is not in English is provided herewith.

☐ Pursuant to MPEP 609(B), an English language copy of a foreign search report is submitted herewith to satisfy the requirement for a concise explanation where non-English language information is cited in the search report.

-- OR --

☐ A concise explanation of the relevance of each patent, publication or other information provided that is not in English is as follows: _____

☐ Pursuant to 37 CFR §1.98(a) (3) (ii), a copy of a translation, or a portion thereof, of the non-English language reference(s) is provided herewith.

H. ☐ *37 CFR §1.98(d).* Copies of patents, publications and pending U.S. patent applications, or other information specified in 37 C.F.R. § 1.98(a) are not provided herewith because:

☐ Pursuant to 37 CFR §1.98(d)(1) the information was previously submitted in an Information Disclosure Statement, or cited by examiner for another application under which this application claims priority for an earlier effective filing date under 35 U.S.C. 120.

Application in which the information was submitted: _____

Information Disclosure Statement(s) filed on: _____

AND

☐ The information disclosure statement submitted in the earlier application complied with paragraphs (a) through (c) of 37 CFR §1.98.

I. ☒ *Fee Authorization*. The Commissioner is hereby authorized to charge the above-referenced fees of $104.00 and charge any additional fees or credit any overpayment associated with this communication to Deposit Account No. 07-1896 (Docket No. 438558-758053).

Respectfully submitted,

Dated: April 15, 2024

/Erin M. Gaffney/

Erin M. Gaffney, Ph.D.
Registration No. 81,479

DLA PIPER LLP (US)
701 Fifth Avenue, Suite 6900
Seattle, Washington 98104-7029
Tel: (206) 839-4800
Fax (206) 839-4801
CUSTOMER NO.: 187495

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	1629
Examiner Name	RAYMOND J HENLEY III
Attorney Docket Number	438558-758053

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	001	US-20160045502-A1	02-18-2016	BROWN; Dennis M.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]–Number[4]–Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	EP-1731142-A1	12-13-2006	DEXCEL PHARMA TECHNOLOGIES LTD [IL]		☐
	002	EP-2101731-A2	09-23-2009	JINA PHARMACEUTICALS INC [US]		☐
	003	EP-2508174-A1	10-10-2012	SOVIC BRKICIC LJILJANA [HR], et al.		☐
	004	WO-2012089677-A1	07-05-2012	LICONSA LABORATORIOS SA [ES], et al.		☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

ACTIVE\1602736535.1

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Application Number	18/128,536
				Filing Date	03-30-2023
				First Named Inventor	QUAY; Steven C.
				Art Unit	1629
				Examiner Name	RAYMOND J HENLEY III
Sheet	2	of	3	Attorney Docket Number	438558-758053

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	001	ALI et al., Endoxifen is a new potent inhibitor of PKC: A potential therapeutic agent for bipolar disorder. Bioorganic & Medicinal Chemistry Letters 20(8): 2665-2667 (2010).	☐
	002	ELKINS P., et al., "Characterization of the Isomeric Configuration and Impurities of (Z)-endoxifen by 2D NMR, High Resolution LC-MS, and Quantitative HPLC Analysis," Journal of Pharmaceutical and Biomedical Analysis, January 2014; vol. 88 pp. 174-179.	☐
	003	European Application No. 20834248.5 Extended Search Report dated June 29, 2023.	☐
	004	"Hardness of Tablet Chart," The 2nd paragraph under the section "Bending Test, 5 August 2023, 26 pages.	☐
	005	JINA PHARMACEUTICALS INC., "IMPROVED PHARMACEUTICAL COMPOSITION OF ENDOXIFEN & PREPARATION THEREOF," 2015, 46 pages.	☐
	006	KU et al., "Performance qualification of a new hypromellose capsule: Part I. Comparative evaluation of physical, mechanical and processability quality attributes of Vcaps Plus, Quali-V and gelatin capsules." International Journal of Pharmaceutics 386: 30-41 (2010).	☐
	007	LIM Y.C., et al., "Endoxifen (4-Hydroxy-N-Desmethyl-Tamoxifen) has Anti-Estrogenic Effects in Breast Cancer Cells with Potency Similar to 4-Hydroxy-Tamoxifen," Cancer Chemother Pharmacol, 2005, Vol. 55, pp. 471-478.	☐
	008	SARAVANAN M. et al., "The Effect of Tablet Formulation and Hardness on in Vitro Release of Cephalexin from Eudragit L100 Based Extended Release Tablets," Biol. Pharm. Bull., April 2002, Vol. 25, No. 4, pp. 541-545.	☐
	009	ZHENG et al., Elimination of antiestrogenic effects of active tamoxifen metabolites by glucuronidation. Drug Metab Dispos. 35(10): 1942-1948 (2007).	☐

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

ACTIVE\1602736535.1

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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Application Number	18/128,536
				Filing Date	03-30-2023
				First Named Inventor	QUAY; Steven C.
				Art Unit	1629
				Examiner Name	RAYMOND J HENLEY III
Sheet	3	of	3	Attorney Docket Number	438558-758053

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Erin M. Gaffney/	Date (YYYY-MM-DD)	2024-04-15
Name/Print	Erin M. Gaffney, Ph.D.	Registration Number	81,479

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/128,536	04/15/2024 08:50:41 PM Z ET	438558-758053

Title of Invention

METHODS FOR MAKING AND USING ENDOXIFEN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1025	FILED BY	Christina Campbell
PATENT CENTER #	65103358	AUTHORIZED BY	Erin Gaffney
CUSTOMER #	187495	FILING DATE	03/30/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Steven C. Quay

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 071896	E20244EK51146416	Christina Campbell

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
071896	37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2806	SUBMISSION OF AN INFORMATION DISCLOSURE STATEMENT	104.00	1	104.00
			TOTAL AMOUNT:	$104.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/128,536	**04/15/2024 08:50:41 PM Z ET**	**438558-758053**

Title of Invention

METHODS FOR MAKING AND USING ENDOXIFEN

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CUSTOMER #	187495	FIRST NAMED INVENTOR	Steven C. Quay
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Erin Gaffney

Documents

TOTAL DOCUMENTS: 18

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
438558-758053- IDS-Transmittal.pdf		4	Letter specifying the conditions for filing under 37 CFR 1.97	156 KB
438558-758053-repsonse.pdf		9	-	153 KB
438558-758053-repsonse-A....pdf	(1-1)	1	Amendment/Request for Reconsideration-After Non-Final Rejection	104 KB
438558-758053-repsonse-CLM.pdf	(2-7)	6	Claims	145 KB
438558-758053-repsonse-REM.pdf	(8-9)	2	Applicant Arguments/Remarks Made in an Amendment	105 KB

EP2508174A1_EFS.pdf	27	Foreign Reference	1549 KB
SARAVANAN_The_Effect_of_Tablet_2002_5pgs_EFS.pdf	5	Non Patent Literature	168 KB
EP1731142A1_EFS.pdf	47	Foreign Reference	2414 KB
Z-ALI-ENDOXIFEN-2655-2667.pdf	3	Non Patent Literature	220 KB
Z-ESR-20834248-29Jun2023.pdf	7	Non Patent Literature	380 KB
WO2012089677A1_EFS.pdf	21	Foreign Reference	875 KB
Hardness_of_Tablet_Chart_2023_26pgs_EFS.pdf	26	Non Patent Literature	3347 KB
Z-LIM-ENDOXIFEN-471-478.pdf	8	Non Patent Literature	357 KB
ELKINS_Characterization_2014_16pgs_EFS.pdf	16	Non Patent Literature	5330 KB
Z-KU-30-41.pdf	12	Non Patent Literature	1680 KB
EP2101731A2_EFS.pdf	55	Foreign Reference	12546 KB
Z-ZHENG-ELIMINATION-1942-1948--.pdf	8	Non Patent Literature	2947 KB
438558-758053_IDS_SB08_20230830142048.pdf	3	Information Disclosure Statement (IDS) Form (SB08)	144 KB

Warning: This is not a USPTO supplied IDS fillable form. Data in the form cannot be automatically loaded to other USPTO systems.

IN139MUN2014_EFS--.pdf	46	Non Patent Literature	6752 KB

Intas Exhibit 1002
Page 315 of 408
PGR2025-00043

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
438558-758053- IDS-Transmittal.pdf	2CF79B96835F0F2D5119DBB25E9810CC351194F72689386 41BCDD63902AE5B02FF5595B42562962E16CE90423A3E05B34C4B1B36418839D03B10CF86375A3CB0
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Intas Exhibit 1002
Page 316 of 408
PGR2025-00043

Z-ESR-20834248-29Jun2023.pdf	C05FE6C38CA22DFF181E20951E689FC4C002BD5F5F974D77964B401C5508DCFC4FF67759AF593D60334DEA1F7C8AE8C5D658D5A0467EF24A37692A2358B803F1
WO2012089677A1_EFS.pdf	F6917527344A2672452CE6EFF9B1F3A96ABB156A5B10B2E0A4EC543EAE99B4F1D11AAB7B003F6AFCCD3BCBF61123A1B1E517B25336ED0CDF0BB0774D265935DD
Hardness_of_Tablet_Chart_2023_26pgs_EFS.pdf	07DD7DB29AC9B00FED51FDF6A2916629D7562DE58E71ABD229DA7CC020E81246F2D17A3ED36335A486623086C49F7B1AF670414963EF09593347234B6949EE3F
Z-LIM-ENDOXIFEN-471-478.pdf	0AFB53D138AB41B8EC1D41A22D94327E37EECE3D9B5A3920B32C3B0A5E0C98AE548D473D279E63EF891415E1C645DC3C4A178D9FD09E503AE21D01CD6651631C
ELKINS_Characterization_2014_16pgs_EFS.pdf	ADE601DC22583D9C800904A9045C39EEFB755048A3F960328EC17E67AFFBED9EFCE5F01864E0B34F9B14EB5C1F8B69B5C20C38EEAA98E0E7BE03C6ED6737FECF
Z-KU-30-41.pdf	CE1625DC295A362AC44BF0C290564D721F9D24059EE1425F41EC613F3F4170CEC3D58B4195CBBD1B912B473FB0596AAE996708E25B9019879EF595AE947C2D9E
EP2101731A2_EFS.pdf	8F10F4A2F3E3266A044EEF2435F8679F699B51935397EFE6239250F6DAA455B18CCB7A6242868DCB51466F4A14E7A74A40EC7C09EA5AADCB79366F22D818FFF0
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438558-758053_IDS_SB08_20230830142048.pdf	6306D0A81F1AD5B8186D82612E64D2BB8E2D83D7573BAAFDDE7BCAAA6ECE8026327D56ECA15528898 4C2AFFC20397CCE66B12E87C7571E32FB25C16F1F895497
IN139MUN2014_EFS--.pdf	4C11468EA0D1C48DEA16C4781CD18474F788150B60134A3160869ADE8ED626B31B96122199390F58E18C6BB3AF9669CF514FF117ECE5D032829D9608E441CE0A

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

187495 7590 05/03/2024

DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

EXAMINER	
HENLEY III, RAYMOND J	
ART UNIT	**PAPER NUMBER**
1629	

DATE MAILED: 05/03/2024

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/128,536	03/30/2023	Steven C. Quay	438558-758053	1025

TITLE OF INVENTION: METHODS FOR MAKING AND USING ENDOXIFEN

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	08/05/2024

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 40% the amount of undiscounted fees, and micro entity fees are 20% the amount of undiscounted fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

187495 7590 05/03/2024

DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/128,536	03/30/2023	Steven C. Quay	438558-758053	1025

TITLE OF INVENTION: METHODS FOR MAKING AND USING ENDOXIFEN

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	08/05/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
HENLEY III, RAYMOND J	1629	514-651000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1_____
2_____
3_____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. Fees submitted: ❑Issue Fee ❑Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

❑ Electronic Payment via the USPTO patent electronic filing system ❑ Enclosed check ❑ Non-electronic payment by credit card (Attach form PTO-2038)

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

❑ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

❑ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

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UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/128,536	03/30/2023	Steven C. Quay	438558-758053	1025

187495 7590 05/03/2024

DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

EXAMINER	
HENLEY III, RAYMOND J	
ART UNIT	PAPER NUMBER
1629	

DATE MAILED: 05/03/2024

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/ owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013).
https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;
2) a federal, state, local, or international agency, in response to its request;
3) a contractor of the USPTO having need for the information in order to perform a contract;
4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;
5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;
6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;
7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;
8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));
9) the Office of Personnel Management (OPM) for personnel research purposes; and
10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

Notice of Allowability	Application No. 18/128,536	Applicant(s) Quay et al.	
	Examiner RAYMOND J HENLEY III	Art Unit 1629	AIA (FITF) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☑ This communication is responsive to Applicant's communication filed April 15, 2024.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

3. ☑ The allowed claim(s) is/are 158-201 . As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information , please see **http://www.uspto.gov/patents/init_events/pph/index.jsp** or send an inquiry to **PPHfeedback@uspto.gov.**

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some* c) ☐ None of the:

   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____ .

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____ .

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☑ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date April 15, 2024.
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material _____.
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date. _____.
5. ☐ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/RAYMOND J HENLEY III/
Primary Examiner, Art Unit 1629

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	**Art Unit**
	RAYMOND J HENLEY III	1629

CPC							
Symbol						**Type**	**Version**
C07C	/	217	/	18		F	2013-01-01
C07C	/	213	/	10		I	2013-01-01
A61K	/	9	/	0053		A	2013-01-01
A61K	/	45	/	06		A	2013-01-01
C07B	/	2200	/	13		A	2013-01-01

CPC Combination Sets								
Symbol					**Type**	**Set**	**Ranking**	**Version**
	/		/					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	44	
/RAYMOND J HENLEY III/ Primary Examiner, Art Unit 1629	24 April 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20240424

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	**Art Unit**
	RAYMOND J HENLEY III	1629

INTERNATIONAL CLASSIFICATION				
CLAIMED				
A61K	/	31	/	135

NON-CLAIMED				
	/		/	

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
514	648

CROSS REFERENCES(S)						
CLASS	**SUBCLASS (ONE SUBCLASS PER BLOCK)**					

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	44	
/RAYMOND J HENLEY III/ Primary Examiner, Art Unit 1629	24 April 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office — Part of Paper No.: 20240424

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Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	**Art Unit**
	RAYMOND J HENLEY III	1629

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIMS

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

NONE		**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	44	
/RAYMOND J HENLEY III/ Primary Examiner, Art Unit 1629	24 April 2024	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	NONE

U.S. Patent and Trademark Office Part of Paper No.: 20240424

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PGR2025-00043

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	Art Unit
	RAYMOND J HENLEY III	1629

CPC - Searched*		
Symbol	**Date**	**Examiner**
A61K 31/135	11/07/2023	RJH
updated	04/24/2024	RJH

CPC Combination Sets - Searched*		
Symbol	**Date**	**Examiner**

US Classification - Searched*			
Class	**Subclass**	**Date**	**Examiner**
514	648	11/07/2023	RJH
	updated	04/24/2024	RJH

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	**Date**	**Examiner**
Reviewed related applications	11/07/2023	RJH
PE2E/PALM applicant/inventor search	11/07/2023	RJH
STN art search, (summary attached)	11/07/2023	RJH
updated	04/24/2024	RJH

Interference Search			
US Class/CPC Symbol	**US Subclass/CPC Group**	**Date**	**Examiner**
	See STN search noted above	04/24/2024	RJH

/RAYMOND J HENLEY III/ Primary Examiner, Art Unit 1629	

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	Art Unit
	RAYMOND J HENLEY III	1629

✓	Rejected	-	Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

CLAIMS

☑ Claims renumbered in the same order as presented by applicant ☐ CPA ☑ T.D. ☐ R.1.47

CLAIM		DATE								
Final	Original	11/07/2023	04/24/2024							
	1	-	-							
	2	-	-							
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PGR2025-00043

Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	**Art Unit**
	RAYMOND J HENLEY III	1629

CLAIM		DATE								
Final	Original	11/07/2023	04/24/2024							
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Page 328 of 408
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	**Art Unit**
	RAYMOND J HENLEY III	1629

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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	**Art Unit**
	RAYMOND J HENLEY III	1629

CLAIM		DATE								
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Index of Claims	Application/Control No.	Applicant(s)/Patent Under Reexamination
	18/128,536	Quay et al.
	Examiner	**Art Unit**
	RAYMOND J HENLEY III	1629

CLAIM		DATE								
Final	Original	11/07/2023	04/24/2024							
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	200	✓	=							
	201	✓	=							

Intas Exhibit 1002
Page 331 of 408
PGR2025-00043

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                 D SET

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L2               1 SEA SPE=ON  ABB=ON  PLU=ON  ENDOXIFEN/CN

      FILE 'HCAPLUS' ENTERED AT 09:41:40 ON 07 NOV 2023
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L4           43792 SEA SPE=ON  ABB=ON  PLU=ON  ENTERIC
L5              12 SEA SPE=ON  ABB=ON  PLU=ON  L3 (P) L4
L6              49 SEA SPE=ON  ABB=ON  PLU=ON  Z (W) ENDOXIFEN
L7               4 SEA SPE=ON  ABB=ON  PLU=ON  L5 AND L6

      FILE 'USPATFULL' ENTERED AT 09:42:53 ON 07 NOV 2023
L8              10 SEA SPE=ON  ABB=ON  PLU=ON  L5 AND L6
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Bibliographic Data

Application No: 18/128,536

Foreign Priority claimed: ○ Yes ◉ No

35 USC 119 (a-d) conditions met: ☐ Yes ☑ No ☐ Met After Allowance

Verified and Acknowledged: /RAYMOND J HENLEY III/ Examiner's Signature | Initials

Title: METHODS FOR MAKING AND USING ENDOXIFEN

FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
03/30/2023	514	1629	438558-758053
RULE			

APPLICANTS

Atossa Therapeutics, Inc.,

INVENTORS

Steven C. Quay, Seattle, WA, UNITED STATES

Yao-Lin Sun, Tainan City, TAIWAN

LungHu Wang, Kaohsiung City, TAIWAN

ChangJung Wu, Kaohsiung City, TAIWAN

ChuanDer Huang, Tainan City, TAIWAN

CONTINUING DATA

This application is a CON of 18090757 12/29/2022 PAT 11680036

18090757 is a CON of 17580428 01/20/2022 PAT 11572334

17580428 is a CON of 16641985 02/25/2020 PAT 11261151

16641985 is a 371 of PCT/US18/50272 09/10/2018

PCT/US18/50272 has PRO of 62693885 07/03/2018

PCT/US18/50272 has PRO of 62624787 01/31/2018

PCT/US18/50272 has PRO of 62556884 09/11/2017

PCT/US18/50272 has PRO of 62556799 09/11/2017

FOREIGN APPLICATIONS

IF REQUIRED, FOREIGN LICENSE GRANTED**

05/02/2023

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STATE OR COUNTRY

UNITED STATES

ADDRESS

DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104
UNITED STATES

FILING FEE RECEIVED

$1,944

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 1 of 3

Complete if Known	
Application Number	18/128,536
Filing Date	03-30-2023
First Named Inventor	QUAY; Steven C.
Art Unit	1629
Examiner Name	RAYMOND J HENLEY III
Attorney Docket Number	438558-758053

U. S. PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Document Number Number-Kind Code[2] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	001	US-20160045502-A1	02-18-2016	BROWN; Dennis M.	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.[1]	Foreign Patent Document Country Code[3]–Number[4]–Kind Code[5] (if known)	Publication Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages Or Relevant Figures Appear	T[6]
	001	EP-1731142-A1	12-13-2006	DEXCEL PHARMA TECHNOLOGIES LTD [IL]		☐
	002	EP-2101731-A2	09-23-2009	JINA PHARMACEUTICALS INC [US]		☐
	003	EP-2508174-A1	10-10-2012	SOVIC BRKICIC LJILJANA [HR], et al.		☐
	004	WO-2012089677-A1	07-05-2012	LICONSA LABORATORIOS SA [ES], et al.		☐

Examiner Signature	/RAYMOND J HENLEY III/ (04/24/2024)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] See Kinds Codes of USPTO Patent Documents at www.uspto.gov or MPEP 901.04. [3] Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). [4] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [5] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [6] Applicant is to place a check mark here if English language Translation is attached.

ACTIVE\1602736535.1

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.J.H/

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Application Number	18/128,536
				Filing Date	03-30-2023
				First Named Inventor	QUAY; Steven C.
				Art Unit	1629
				Examiner Name	RAYMOND J HENLEY III
Sheet	2	of	3	Attorney Docket Number	438558-758053

NON-PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.[1]	Include name of the author(in CAPITAL LETTERS),title of the article(when appropriate), title of the item (book,magazine,journal,serial,symposium,catalog,etc.),date,page(s),volume-issue number(s),publisher, city and/or country where published.	T[2]
	001	ALI et al., Endoxifen is a new potent inhibitor of PKC: A potential therapeutic agent for bipolar disorder. Bioorganic & Medicinal Chemistry Letters 20(8): 2665-2667 (2010).	☐
	002	ELKINS P., et al., "Characterization of the Isomeric Configuration and Impurities of (Z)-endoxifen by 2D NMR, High Resolution LC-MS, and Quantitative HPLC Analysis," Journal of Pharmaceutical and Biomedical Analysis, January 2014; vol. 88 pp. 174-179.	☐
	003	European Application No. 20834248.5 Extended Search Report dated June 29, 2023.	☐
	004	"Hardness of Tablet Chart," The 2nd paragraph under the section "Bending Test, 5 August 2023, 26 pages.	☐
	005	JINA PHARMACEUTICALS INC., "IMPROVED PHARMACEUTICAL COMPOSITION OF ENDOXIFEN & PREPARATION THEREOF," 2015, 46 pages.	☐
	006	KU et al., "Performance qualification of a new hypromellose capsule: Part I. Comparative evaluation of physical, mechanical and processability quality attributes of Vcaps Plus, Quali-V and gelatin capsules." International Journal of Pharmaceutics 386: 30-41 (2010).	☐
	007	LIM Y.C., et al., "Endoxifen (4-Hydroxy-N-Desmethyl-Tamoxifen) has Anti-Estrogenic Effects in Breast Cancer Cells with Potency Similar to 4-Hydroxy-Tamoxifen," Cancer Chemother Pharmacol, 2005, Vol. 55, pp. 471-478.	☐
	008	SARAVANAN M. et al., "The Effect of Tablet Formulation and Hardness on in Vitro Release of Cephalexin from Eudragit L100 Based Extended Release Tablets," Biol. Pharm. Bull., April 2002, Vol. 25, No. 4, pp. 541-545.	☐
	009	ZHENG et al., Elimination of antiestrogenic effects of active tamoxifen metabolites by glucuronidation. Drug Metab Dispos. 35(10): 1942-1948 (2007).	☐

Examiner Signature	/RAYMOND J HENLEY III/ (04/24/2024)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. [1] Applicant's unique citation designation number (optional). [2] Applicant is to place a check mark here if English language Translation is attached.

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ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /R.J.H/

Substitute for form 1449/PTO				Complete if Known	
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Use as many sheets as necessary)				Application Number	18/128,536
				Filing Date	03-30-2023
				First Named Inventor	QUAY; Steven C.
				Art Unit	1629
				Examiner Name	RAYMOND J HENLEY III
Sheet	3	of	3	Attorney Docket Number	438558-758053

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Erin M. Gaffney/	Date (YYYY-MM-DD)	2024-04-15
Name/Print	Erin M. Gaffney, Ph.D.	Registration Number	81,479

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/128,536	**05/09/2024 07:32:35 PM Z ET**	**438558-758053**

Title of Invention

METHODS FOR MAKING AND USING ENDOXIFEN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1025	FILED BY	Hillary Pratt
PATENT CENTER #	65450948	FILING DATE	03/30/2023
CUSTOMER #	187495	FIRST NAMED INVENTOR	Steven C. Quay
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Erin Gaffney

Documents

TOTAL DOCUMENTS: 3

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
438558-758053_General_POA.pdf	1	Power of Attorney	57 KB
438558-758053_Statement_373c.pdf	3	Assignee showing of ownership per 37 CFR 3.73	249 KB
438558-758053_Marked-ADS_final_.pdf	10	Application Data Sheet	1346 KB

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Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/AIA/80 (07-17)
Approved for use through 09/30/2021. OMB 0651-0035
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

[X] Practitioners associated with Customer Number: 187495

OR

[ ] Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used).

Name	Registration Number	Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

[X] The address associated with Customer Number: 187495

OR

[ ]

Firm or individual name		
Address		
City	State	Zip
Country		
Telephone	Email	

Assignee name and address: Atossa Therapeutics, Inc.
107 Spring Street
Seattle, Washington 98104

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

Signature Heather Rees	Date 11/6/2023
Name Heather Rees	Telephone
Title SVP, Finance & Principal Accounting Officer	

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 18 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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STATEMENT UNDER 37 CFR 3.73(c)

First Named Inventor/Patent Owner: Atossa Therapeutics, Inc.

Application No./Patent No.: 18/128,536 Filed/Issue Date: March 30, 2023

Titled: METHODS FOR MAKING AND USING ENDOXIFEN

Atossa Therapeutics, Inc., a corporation

(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☑ The assignee of the entire right, title, and interest.

2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):

   ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.

   ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

   Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (*e.g.*, bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached*.

B. ☑ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:

   1. From: STEVEN C. QUAY To: ATOSSA THERAPEUTICS, INC.

      The document was recorded in the United States Patent and Trademark Office at Reel 064165, Frame 0532, or for which a copy thereof is attached*.

   2. From: YAO-LIN SUN, LUNGHU WANG, CHANGJUNG WU, CHUANDER HUANG To: KRISAN BIOTECH CO., LTD.

      The document was recorded in the United States Patent and Trademark Office at Reel 064165, Frame 0617, or for which a copy thereof is attached*.

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STATEMENT UNDER 37 CFR 3.73(c)

3. From: KRISAN BIOTECH CO., LTD. To: ATOSSA THERAPEUTICS, INC.

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4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
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5. From: _____ To: _____

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Reel _____, Frame _____, or for which a copy thereof is attached*.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached*.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☑ *As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Erin M. Gaffney/	May 9, 2024
Signature	Date
Erin M. Gaffney, Ph.D.	81,479
Printed or Typed Name	Title or Registration Number

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. The United States Patent and Trademark Office (USPTO) collects the information in this record under authority of 35 U.S.C. 2. The USPTO's system of records is used to manage all applicant and owner information including name, citizenship, residence, post office address, and other information with respect to inventors and their legal representatives pertaining to the applicant's/owner's activities in connection with the invention for which a patent is sought or has been granted. The applicable Privacy Act System of Records Notice for the information collected in this form is COMMERCE/PAT-TM-7 Patent Application Files, available in the Federal Register at 78 FR 19243 (March 29, 2013). https://www.govinfo.gov/content/pkg/FR-2013-03-29/pdf/2013-07341.pdf

Routine uses of the information in this record may include disclosure to:

1) law enforcement, in the event that the system of records indicates a violation or potential violation of law;

2) a federal, state, local, or international agency, in response to its request;

3) a contractor of the USPTO having need for the information in order to perform a contract;

4) the Department of Justice for determination of whether the Freedom of Information Act (FOIA) requires disclosure of the record;

5) a Member of Congress submitting a request involving an individual to whom the record pertains, when the individual has requested the Member's assistance with respect to the subject matter of the record;

6) a court, magistrate, or administrative tribunal, in the course of presenting evidence, including disclosures to opposing counsel in the course of settlement negotiations;

7) the Administrator, General Services Administration (GSA), or their designee, during an inspection of records conducted by GSA under authority of 44 U.S.C. 2904 and 2906, in accordance with the GSA regulations and any other relevant (i.e., GSA or Commerce) directive, where such disclosure shall not be used to make determinations about individuals;

8) another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c));

9) the Office of Personnel Management (OPM) for personnel research purposes; and

10) the Office of Management and Budget (OMB) for legislative coordination and clearance.

If you do not furnish the information requested on this form, the USPTO may not be able to process and/or examine your submission, which may result in termination of proceedings, abandonment of the application, and/or expiration of the patent.

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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	18/128,536
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2:

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Steven	C.	Quay	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Seattle	State/Province	WA	Country of Residence	US

Mailing Address of Inventor:

Address 1	107 Spring Street		
Address 2			
City	Seattle	State/Province	WA
Postal Code	98104	Country	US

Inventor 2 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	Yao-Lin		Sun	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Tainan City	Country of Residence	TW

Mailing Address of Inventor:

Address 1	~~107 Spring Street~~ 4F No. 30, Ln. 31, Sec. 1, Huandong Rd.		
Address 2	Xinshi Dist.		
City	~~Seattle~~ Tainan City	State/Province	~~WA~~
Postal Code	~~98104~~ 741	Country	~~US~~ TW

Inventor 3 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	LungHu		Wang	

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	18/128,536
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Kaohsiung City	Country of Residence	TW

Mailing Address of Inventor:

Address 1	~~107 Spring Street~~ 4F No. 30, Ln. 31, Sec. 1, Huandong Rd.
Address 2	Xinshi Dist.

City	~~Seattle~~ Tainan City	State/Province	~~WA~~
Postal Code	~~98104~~ 741	**Country**	~~US~~ TW

Inventor 4 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	ChangJung		Wu	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Kaohsiung City	Country of Residence	TW

Mailing Address of Inventor:

Address 1	~~107 Spring Street~~ 4F No. 30, Ln. 31, Sec. 1, Huandong Rd.
Address 2	Xinshi Dist.

City	~~Seattle~~ Tainan City	State/Province	~~WA~~
Postal Code	~~98104~~ 741	**Country**	~~US~~ TW

Inventor 5 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	ChuanDer		Huang	

Residence Information (Select One) ○ US Residency ◉ Non US Residency ○ Active US Military Service

City	Tainan City	Country of Residence	TW

Mailing Address of Inventor:

Address 1	~~107 Spring Street~~ 4F No. 30, Ln. 31, Sec. 1, Huandong Rd.
Address 2	Xinshi Dist.

City	~~Seattle~~ Tainan City	State/Province	~~WA~~
Postal Code	~~98104~~ 741	**Country**	~~US~~ TW

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	18/128,536
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	187495		
Email Address	seattlepatentdocket@us.dlapiper.com	Add Email	Remove Email

Application Information:

Title of the Invention	METHODS FOR MAKING AND USING ENDOXIFEN		
Attorney Docket Number	438558-758053	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)	13	**Suggested Figure for Publication (if any)**	3

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	18/128,536
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	187495		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
18128536	Continuation of	18090757	2022-12-29	11680036	2023-06-20
Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
18090757	Continuation of	17580428	2022-01-20	11572334	2023-02-07
Prior Application Status	Patented			Remove	
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
17580428	Continuation of	16641985	2020-02-25	11261151	2022-03-01
Prior Application Status	Expired		Remove		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
16641985	a 371 of international	PCT/US18/50272	2018-09-10		
Prior Application Status	Expired		Remove		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
PCT/US18/50272	Claims benefit of provisional	62693885	2018-07-03		
Prior Application Status	Expired		Remove		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
PCT/US18/50272	Claims benefit of provisional	62624787	2018-01-31		
Prior Application Status	Expired		Remove		
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)		
PCT/US18/50272	Claims benefit of provisional	62556799	2017-09-11		

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	18/128,536
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
PCT/US18/50272	Claims benefit of provisional	62556884	2017-09-11
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.			

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX)[i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

			Remove
Application Number	Country[i]	Filing Date (YYYY-MM-DD)	Access Code[i] (if applicable)
Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.			

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	18/128,536
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.

☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	18/128,536
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

(•) Assignee	( ) Legal Representative under 35 U.S.C. 117	( ) Joint Inventor
( ) Person to whom the inventor is obligated to assign.	( ) Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. [x]

Organization Name	Atossa Therapeutics, Inc.

Mailing Address Information For Applicant:

Address 1	107 Spring Street		
Address 2			
City	Seattle	**State/Province**	WA
Country	US	Postal Code	98104
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	18/128,536
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

Assignee 1

Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

If the Assignee or Non-Applicant Assignee is an Organization check here. ☐

Prefix	**Given Name**	Middle Name	**Family Name**	Suffix

Mailing Address Information For Assignee including Non-Applicant Assignee:

Address 1			
Address 2			
City		**State/Province**	
Country		Postal Code	
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Erin M. Gaffney/			Date (YYYY-MM-DD)	2024-05-09
First Name	Erin M.	Last Name	Gaffney, Ph.D.	Registration Number	81,479

Additional Signature may be generated within this form by selecting the Add button.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	438558-758053
	Application Number	18/128,536
Title of Invention	METHODS FOR MAKING AND USING ENDOXIFEN	

This collection of information is required by 37 CFR 1.76. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1 The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3 A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent CooperationTreaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

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United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
18/128,536	03/30/2023	1629	1856	438558-758053	44	2

CONFIRMATION NO. 1025

REPLACEMENT FILING RECEIPT

187495
DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

Date Mailed: 05/16/2024

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please submit a written request for a corrected Filing Receipt, including a properly marked-up ADS showing the changes with strike-through for deletions and underlining for additions. If you received a "Notice to File Missing Parts" or other Notice requiring a response for this application, please submit any request for correction to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections provided that the request is grantable.

Inventor(s)

Steven C. Quay, Seattle, WA;
Yao-Lin Sun, Tainan City, TAIWAN;
LungHu Wang, Kaohsiung City, TAIWAN;
ChangJung Wu, Kaohsiung City, TAIWAN;
ChuanDer Huang, Tainan City, TAIWAN;

Applicant(s)

Atossa Therapeutics, Inc., Seattle, WA;

Power of Attorney: The patent practitioners associated with Customer Number 187495

Domestic Priority data as claimed by applicant

This application is a CON of 18/090,757 12/29/2022 PAT 11,680,036
which is a CON of 17/580,428 01/20/2022 PAT 11,572,334
which is a CON of 16/641,985 02/25/2020 PAT 11,261,151
which is a 371 of PCT/US18/50272 09/10/2018
which claims benefit of 62/693,885 07/03/2018
and claims benefit of 62/624,787 01/31/2018
and claims benefit of 62/556,799 09/11/2017
and claims benefit of 62/556,884 09/11/2017

Foreign Applications for which priority is claimed (You may be eligible to benefit from the Patent Prosecution Highway program at the USPTO. Please see http://www.uspto.gov for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 05/02/2023
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 18/128,536**
Projected Publication Date: 11/16/2023
Non-Publication Request: No
Early Publication Request: No
**** SMALL ENTITY ****
Title

METHODS FOR MAKING AND USING ENDOXIFEN

Preliminary Class

514

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign

patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

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Title 37, Code of Federal Regulations, 5.11 & 5.15

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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
18/128,536	03/30/2023	Steven C. Quay	438558-758053

CONFIRMATION NO. 1025

187495
DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

POA ACCEPTANCE LETTER

OC000000072637627

Date Mailed: 05/16/2024

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/09/2024.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at **(571) 272-4000** or **(571) 272-4200** or **1-888-786-0101**.

/cgarner/

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on May 29, 2024.

DLA PIPER LLP (US)

By: /Hillary Pratt/

Attorney Docket No.: 438558-758053

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Steven C. Quay et al. Application No.: 18/128,536 Filed: March 30, 2023 For: METHODS FOR MAKING AND USING ENDOXIFEN Customer No. 187495	Confirmation No. 1025 Examiner: RAYMOND J HENLEY III Art Unit: 1629 **AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. § 1.312**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Prior to issuance of the patent, Applicant respectfully requests entry of this amendment under 37 C.F.R. § 1.312 for the above-captioned patent application.

Amendments to the Specification begin on page 2.

Amendments to the Claims are reflected in the listing of claims beginning on page 3.

Remarks begin on page 9.

1609811691.1

Amendments to the Specification:

Please replace paragraph **[0001]** of the Specification with the following amended paragraph:

CROSS-REFERENCE

[0001] This application is a continuation of U.S. Patent Application No. 18/090,757, filed December 29, 2022, now U.S. Patent No. 11,680,036, issued June 20, 2023, which is a continuation of U.S. Application No. 17/580,428, filed January 20, 2022, now U.S. Patent No. 11,572,334, issued February 7, 2023, which is a continuation of U.S. Patent Application No. 16/641,985, filed February 25, 2020, now U.S. Patent No. 11,261,151, issued on March 1, 2022, which is a U.S. National Phase Application under 35 U.S.C. § 371 of International Application No. PCT/US2018/050272, filed September 10, 2018, which claims the benefit of U.S. Provisional Application No. 62/556,799, filed September 11, 2017; U.S. Provisional Application No. 62/556,884, filed September 11, 2017; U.S. Provisional Application No. 62/624,787, filed January 31, 2018; and U.S. Provisional Application No. 62/693,885, filed July 3, 2018, each incorporated herein by reference in their entireties.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings of claims in the application:

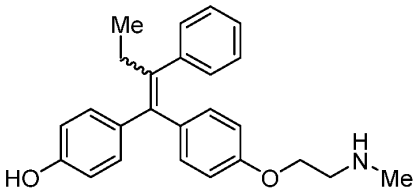
Listing of Claims:

157. (Canceled)

158. (Previously Presented) A composition comprising an endoxifen and an enteric material,

wherein:

the endoxifen comprises a compound of Formula (III):



Formula (III)

or a pharmaceutically acceptable salt thereof; and

at least 90% by weight of the compound of Formula (III) is (*Z*)-endoxifen.

159. (Previously Presented) The composition of claim 158, wherein the pharmaceutically acceptable salt is selected from the group consisting of an: arecoline, besylate, bicarbonate, bitartarate, butylbromide, citrate, camysylate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynapthanoate, isethionate, malate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamaoate (Embonate), pantothenate, phosphate/diphosphate, polygalacuronate, salicylate, stearate, sulfate, tannate, Teoclate, triethiodide, benzathine, clemizole, chloroprocaine, choline, diethylamine, diethanolamine, ethylenediamine, meglumine, piperazine, procaine, aluminum, barium, bismuth, lithium, magnesium, potassium, and zinc salt.

160. (Previously Presented) The composition of claim 158, wherein the pharmaceutically acceptable salt of the compound of Formula (III) is endoxifen gluconate.

161. (Previously Presented) The composition of claim 158, wherein the composition is a delayed-release formulation.

162. (Previously Presented) The composition of claim 158, wherein the composition is a tablet.

163. (Previously Presented) The composition of claim 158, wherein the composition is a capsule.

164. (Previously Presented) The composition of claim 158, wherein the composition is uncoated.

165. (Previously Presented) The composition of claim 158, wherein the composition comprises an enteric coating.

166. (Previously Presented) The composition of claim 158, wherein the composition is formulated as a suspension.

167. (Previously Presented) The composition of claim 166, wherein the suspension comprises a syrup or an elixir.

168. (Previously Presented) The composition of claim 166, wherein the suspension comprises a fluid.

169. (Previously Presented) The composition of claim 168, wherein the fluid comprises an alcohol.

170. (Previously Presented) The composition of claim 169, wherein the alcohol comprises ethanol.

171. (Previously Presented) The composition of claim 166, wherein the suspension comprises an alcohol, a plant oil, a mineral oil, a glycol, an agar, or a mixture thereof.

172. (Previously Presented) The composition of claim 166, wherein the suspension comprises ethanol, mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, vegetable oil, stearic acid, sodium lauryl sulfate, or a mixture thereof.

173. (Previously Presented) The composition of claim 158, wherein the compound of Formula (III) is stable in the composition for at least 10 days at about 25°C.

174. (Previously Presented) The composition of claim 158, formulated such that the composition is resistant to dissolution in an acidic environment for at least 2 hours, as measured in a dissolution test performed according to a method of USP 711.

175. (Previously Presented) The composition of claim 158, formulated such that the composition releases no more than 10% of the (*Z*)-endoxifen over 2 hours in gastric fluid, as measured in a dissolution test performed according to a method of USP 711.

176. (Previously Presented) The composition of claim 158, formulated such that the composition releases at least 50% of the (*Z*)-endoxifen within 8 hours in intestinal fluid, as measured in a dissolution test performed according to a method of USP 711.

177. (Previously Presented) The composition of claim 158, wherein the composition further comprises hydroxypropylmethyl cellulose.

178. (Previously Presented) The composition of claim 158, wherein the composition further comprises a filler.

179. (Previously Presented) The composition of claim 178, wherein the filler comprises a sugar, salt, talc, calcium carbonate, microcrystalline cellulose, methyl cellulose,

carboxymethyl cellulose, kaolin, mannitol, silicic acid, sorbitol, starch, pregelatinized starch, or combinations thereof.

180. (Previously Presented) The composition of claim 158, wherein the composition further comprises a disintegrant.

181. (Previously Presented) The composition of claim 158, wherein the composition further comprises a lubricant.

182. (Previously Presented) The composition of claim 181, wherein the lubricant comprises calcium stearate, magnesium stearate, zinc stearate, mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil, ethyl oleate, ethyl laureate, agar, or combinations thereof.

183. (Previously Presented) The composition of claim 158, wherein the composition comprises from 0.01 mg to 200 mg (*Z*)-endoxifen.

184. (Previously Presented) The composition of claim 158, wherein the composition comprises from 1 mg to 20 mg of (*Z*)-endoxifen.

185. (Previously Presented) The composition of claim 158, wherein the composition comprises from 1 mg to 4 mg of (*Z*)-endoxifen.

186. (Previously Presented) The composition of claim 158, wherein the composition comprises 8 mg of (*Z*)-endoxifen.

187. (Previously Presented) A method of making the composition of claim 166, the method comprising suspending the endoxifen and the enteric material in a fluid.

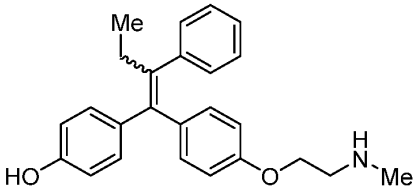
188. (Previously Presented) The method of claim 187, wherein the fluid comprises an alcohol, ethanol, a plant oil, a mineral oil, a glycol, an agar, glycerin, sorbitol, mannitol, polyethylene glycol, vegetable oil, stearic acid, sodium lauryl sulfate, or a mixture thereof.

Intas Exhibit 1002
Page 364 of 408
PGR2025-00043

189. (Previously Presented) A method comprising administering to a subject a composition comprising an endoxifen and an enteric material,

wherein:

the endoxifen comprises a compound of Formula (III):



Formula (III)

or a pharmaceutically acceptable salt thereof; and

at least 90% by weight of the compound of Formula (III) is (*Z*)-endoxifen.

190. (Previously Presented) The method of claim 189, comprising administering 1 mg to 20 mg of (*Z*)-endoxifen.

191. (Previously Presented) The method of claim 189, comprising administering 1 mg to 4 mg of (*Z*)-endoxifen.

192. (Previously Presented) The method of claim 189, comprising administering 8 mg of (*Z*)-endoxifen.

193. (Previously Presented) The method of claim 189, wherein the administering of the composition maintains the subject's plasma endoxifen at a steady state level above 30 nM.

194. (Previously Presented) The method of claim 189, wherein the administering of the composition maintains the subject's plasma endoxifen at a steady state level from 30 nM to 300 nM.

195. (Currently Amended) The method of claim 189, further comprising releasing no more than 10% of the (*Z*)-endoxifen in a stomach of the subject within 2 hours following the ~~administrating~~ administering of the composition.

196. (Currently Amended) The method of claim 189, further comprising releasing at least 50% of the (*Z*)-endoxifen in a small intestine of the subject within 8 hours following the ~~administrating~~ administering of the composition.

197. (Previously Presented) The method of claim 189, further comprising producing an area under curve ($AUC_{0\text{-}inf}$) of (*Z*)-endoxifen in the subject of from 200 hr*ng/mL to 10,000 hr*ng/mL per 4 mg of (*Z*)-endoxifen administered.

198. (Previously Presented) The method of claim 189, further comprising producing a maximum blood plasma concentration (C_{max}) of (*Z*)-endoxifen in the subject of from 14 ng/mL to 62 ng/mL per 4 mg of (*Z*)-endoxifen administered.

199. (Previously Presented) The method of claim 189, further comprising treating a hormone-dependent breast disorder or a hormone-dependent reproductive tract disorder in the subject in need thereof.

200. (Previously Presented) The method of claim 199, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is a benign breast disorder, hyperplasia, atypia, atypical ductal hyperplasia, atypical lobular hyperplasia, increased breast density, gynecomastia, ductal carcinoma *in situ*, lobular carcinoma *in situ*, breast cancer, precocious puberty, McCune-Albright Syndrome, endometrial cancer, ovarian cancer, uterine cancer, cervical cancer, vaginal cancer, or vulvar cancer.

201. (Previously Presented) The method of claim 199, wherein the hormone-dependent breast disorder or the hormone-dependent reproductive tract disorder is tamoxifen-refractory or tamoxifen resistant.

REMARKS

In this Amendment, Applicant amends the Specification to update referenced application information. Applicant also amends claims 195 and 196 solely to correct typographical errors. No new matter has been added.

Further, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 07-1896.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-839-4800.

Respectfully submitted,

Dated: May 29, 2024

/Erin M. Gaffney/

Erin M. Gaffney, Ph.D.
Registration No. 81,479

DLA PIPER LLP (US)
701 Fifth Avenue, Suite 6900
Seattle, Washington 98104-7029
Tel: (206) 839-4800
Fax (206) 839-4801

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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/128,536	**05/29/2024 08:47:02 PM Z ET**	**438558-758053**

Title of Invention

METHODS FOR MAKING AND USING ENDOXIFEN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1025	FILED BY	Hillary Pratt
PATENT CENTER #	65725318	FILING DATE	03/30/2023
CUSTOMER #	187495	FIRST NAMED INVENTOR	Steven C. Quay
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Erin Gaffney

Documents

TOTAL DOCUMENTS: 4

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
438558-758053_312_Amendment.pdf		9	-	187 KB
438558-758053_312_Amendment-A.NA.pdf	(1-1)	1	Amendment after Notice of Allowance (Rule 312)	137 KB
438558-758053_312_Amendment-SPEC.pdf	(2-2)	1	Specification	136 KB
438558-758053_312_Amendment-CLM.pdf	(3-8)	6	Claims	178 KB

Intas Exhibit 1002
Page 369 of 408
PGR2025-00043

438558-758053_312_Amendment-REM.pdf	(9-9)	1	Applicant Arguments/Remarks Made in an Amendment	136 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
438558-758053_312_Amendment.pdf	9D5125E8D2376CB591FFD6F54A0E160B133763116E687318F83D06BC343908C0CA8821D8EA728D330A3970189215ED64A385D7DC974EF381FED627C00769599A
438558-758053_312_Amendment-A.NA.pdf	F4E4615686846C5346149283C36825EE53FB458B64EBE22901D4EF6B7EEEDA5CC057F31B0AC6EA45922018B06CC0A5E6CD38E7C88A864241EBF3D51A9CEE716A
438558-758053_312_Amendment-SPEC.pdf	D50071D403E4180E191A729903640319 88C67D409944C1B060D5F56C198869316E4D56DF254208AE03CE2AA111AFF45E686EEC7ABC6F3580E40A8B6E51680403
438558-758053_312_Amendment-CLM.pdf	E9BCDAA001E86CFE05291335000F439B92832997E21D457BC1AA4EAD3FAFEC07A878E731B206F63D6AF74BFE06BEA9994C8538435B27077DFA120B86E6E30791
438558-758053_312_Amendment-REM.pdf	917BC092F5970706EA0118E211E592122749892A5C9718D2CF0427D8801C29A2B8D2AA130165F2B55C9A47FF7E47040BA22EF575E5D47E6B291B653A224494E9

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

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If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/128,536	03/30/2023	Steven C. Quay	438558-758053	1025

187495 7590 06/10/2024

DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

EXAMINER	
HENLEY III, RAYMOND J	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
06/10/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

seattlepatentdocket@us.dlapiper.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
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Application No. : 18128536
Applicant : Quay
Filing Date : 03/30/2023
Date Mailed : 06/10/2024

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given two (2) months from the mail date of this Notice within which to respond. This time period for reply is extendable under 37 CFR 1.136(a) for only TWO additional MONTHS.

The informalities requiring correction are indicated in the attachment(s). If the informality pertains to the abstract, specification (including claims) or drawings, the informality must be corrected with an amendment in compliance with 37 CFR 1.121 (or, if the application is a reissue application, 37 CFR 1.173). Such an amendment may be filed after payment of the issue fee if limited to correction of informalities noted herein. See Waiver of 37 CFR 1.312 for Documents Required by the Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004). In addition, if the informality is not corrected until after payment of the issue fee, for purposes of 35 U.S.C. 154(b)(1)(iv), "all outstanding requirements" will be considered to have been satisfied when the informality has been corrected. A failure to respond within the above-identified time period will result in the application being ABANDONED.

See attachment(s).

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

/Midel Geronimo/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 18128536 **Drawings filed: 03/30/2023**

IDENTIFICATION OF DRAWING DEFICIENCIES

- [ ] There is a hole or the image thereof within the illustration. FIG(s)
- [ ] The illustration is penetrated or traversed by a solid or broken line that is not intended to be part of the drawing, such as a dark line caused by a flaw in the copying process. FIG(s)
- [ ] An ink stamp or the image thereof obscures part of the illustration. FIG(s)
- [ ] The drawing is marred by black smudges, obliterations, or fax/copier marks (for example, speckles or dots in a substantial portion of the drawing). FIG(s)
- [ ] Figure numbers are duplicated or missing. FIG(s)
- [ ] Drawing sheet or figure is missing. FIG(s)
- [ ] Numbers, letters, or reference characters in the drawing have been crossed out or are illegibly handwritten. FIG(s)
- [X] The character of the lines, numbers, and letters is poor. FIG(s) 2-13
- [ ] The drawing's background shows that the original drawing was made on graph paper or other paper with a pattern or decoration. FIG(s)
- [ ] The FIG. number label is placed in a location that causes the drawing to be read upside down. FIG(s)
- [X] Data, a reference number, or part of the drawing is truncated or missing, or a lead line has no reference number. FIG(s) 2-13
- [ ] The drawing and/or the FIG. label contain(s) foreign language. FIG(s)
- [ ] This utility application contains a photograph of a view that is capable of being illustrated as a line drawing. FIG(s)
- [ ] A petition under 37 CFR 1.84(a)(2) to accept color drawings has been granted, but the brief description of the drawings in the specification does not contain (or has not been amended to contain) the paragraph required by 37 CFR 1.84(a)(2)(iii).
- [ ] This reissue application contains added and/or amended drawings that are not labeled as “New” or “Amended” or “Canceled” as required by 37 CFR 1.173(b)(3). FIG(s)
- [ ] This Design reissue application contains a drawing that is labeled as “Canceled” but is not surrounded by brackets, or a drawing that is surrounded by brackets but is not labeled as “Canceled.” See 37 CFR 1.173(b)(3). FIG(s)
- [ ] OTHER:
- [ ] COMMENTS:

DocCode - SCORE

Placeholder Sheet for Supplemental Content

Application Number: 18128536 Document Date: 06/21/2024

The presence of this form indicates that the following document type was received in electronic format on the date identified above. This document is stored separately from the typical case contents which are stored in image format.

Since this was an electronic submission, there is no physical artifact folder, no artifact folder is recorded and no paper documents or physical media exist.

- Drawing

At the time of document entry (noted above):

- USPTO employees may access this supplemental content via Docket Application Viewer (DAV) or Supplemental Content Viewer (SCV).
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Form Revision Date: March 1, 2024

DocCode - SCORE

SCORE Placeholder Sheet for IFW Content

Application Number: 18128536 Document Date: 06/21/2024

The presence of this form in the IFW record indicates that the following document type was received in electronic format on the date identified above. This content is stored in the SCORE database.

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- Drawing

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- USPTO employees may access SCORE content via DAV or via the SCORE web page.
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Form Revision Date: March 1, 2019

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P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/128,536	**06/21/2024 06:00:40 PM Z ET**	**438558-758053**

Title of Invention

METHODS FOR MAKING AND USING ENDOXIFEN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1025	FILED BY	Hillary Pratt
PATENT CENTER #	66071963	FILING DATE	03/30/2023
CUSTOMER #	187495	FIRST NAMED INVENTOR	Steven C. Quay
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Emma Holland

Documents

TOTAL DOCUMENTS: 5

DOCUMENT		PAGES	DESCRIPTION	SIZE (KB)
438558-758053_Response.pdf		3	-	106 KB
438558-758053_Response-LET..pdf	(1-1)	1	Miscellaneous Incoming Letter	102 KB
438558-758053_Response-DRW.pdf	(2-2)	1	Drawings-only black and white line drawings	101 KB
438558-758053_Response-REM.pdf	(3-3)	1	Applicant Arguments/Remarks Made in an Amendment	101 KB
438558-758053_Notice_Correct_Dra		3	Drawings-only black and white line drawings	109 KB

Intas Exhibit 1002
Page 377 of 408
PGR2025-00043

wings.pdf			
438558-758053_Replacement_Figures_.pdf	12	Drawings-only black and white line drawings	2860 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
438558-758053_Response.pdf	A065D978608786C6C544603DDFE3486099250180A5B11DAFA59E4650EF27437DEE549B4FBC230BE85FE3A016D83E364E50FFE05D13BAF22017DAB840795BC94D
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438558-758053_Replacement_Figures_.pdf	8F45BCA3322431753BFDC17AB96904658CA304EDA26BE5341A940344F706AB1F597F34AA3B49909415DF1664732F6A46A028F78FDBA575BB53BB8FD3443762AA

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Intas Exhibit 1002
Page 379 of 408
PGR2025-00043

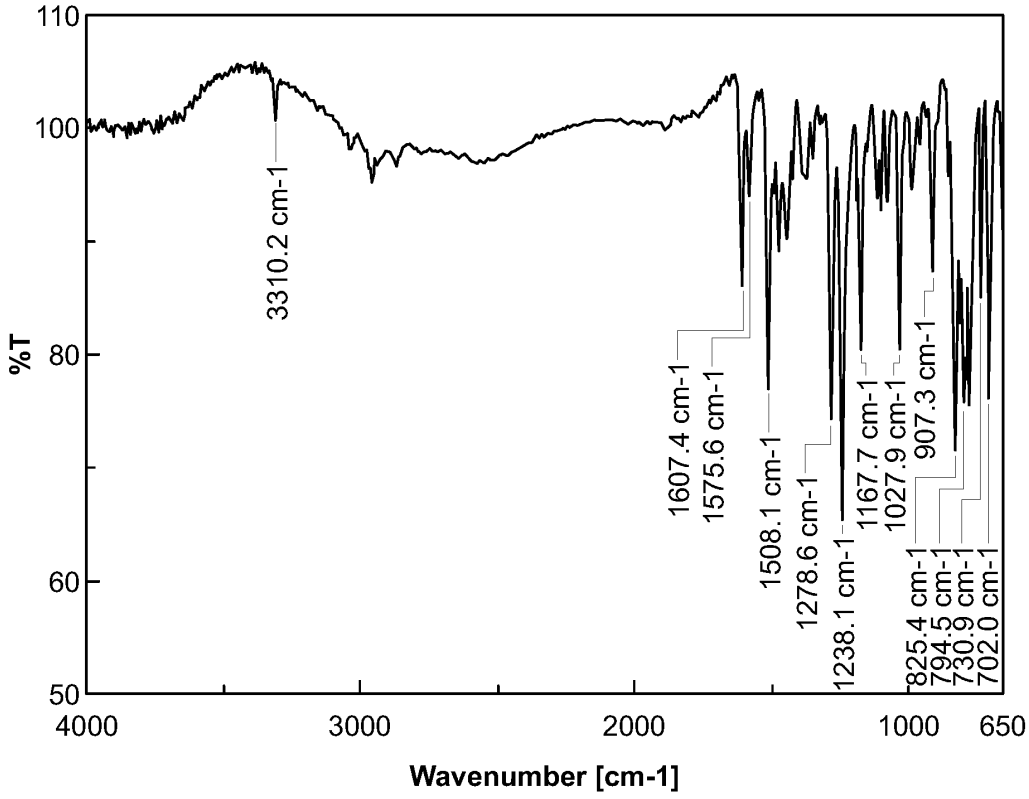


FIG. 2

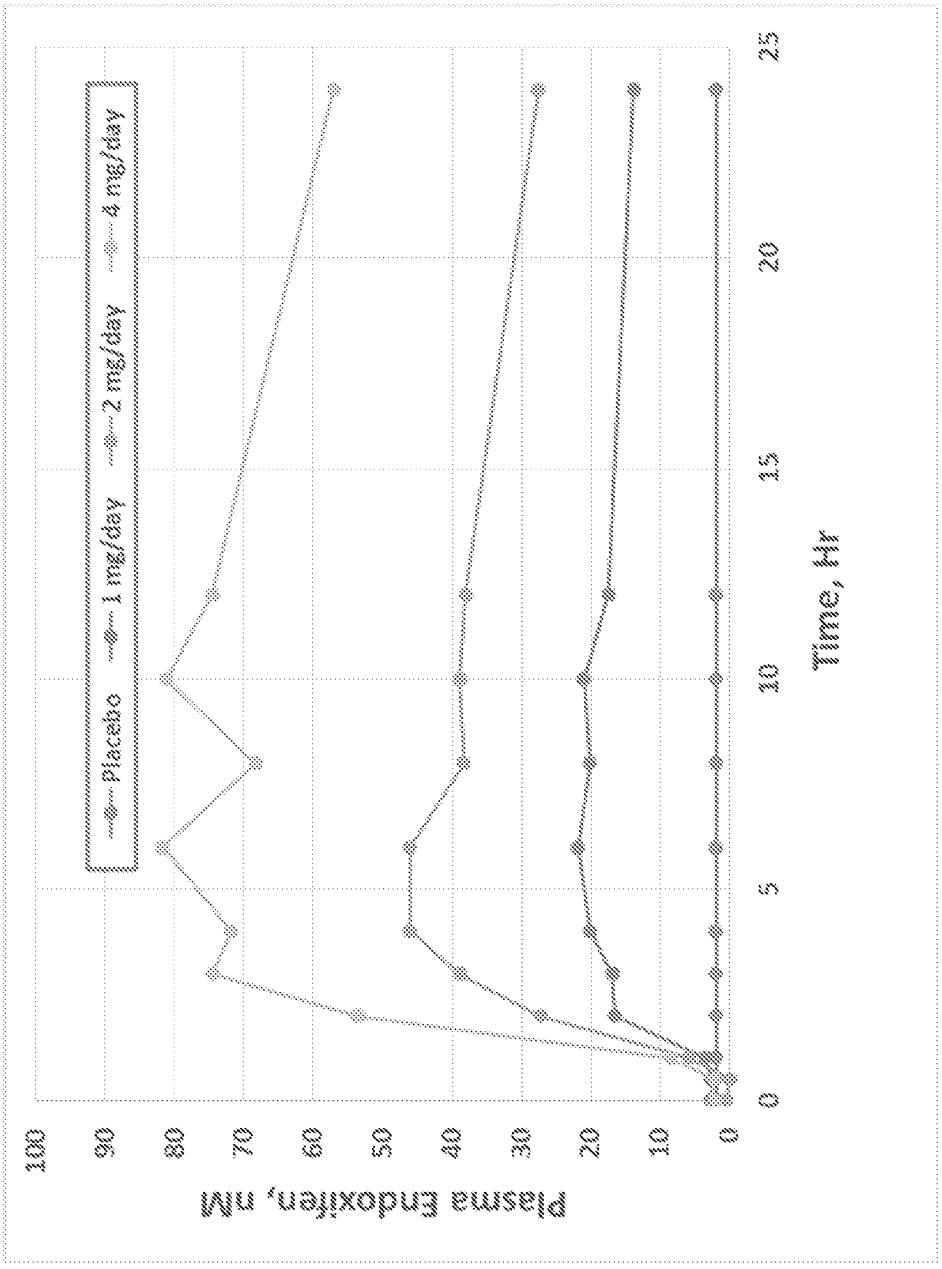

Plasma Endoxifen, nM
100
90
80
70
60
50
40
30
20
10
0
0
5
10
15
20
25
Time, Hr
Placebo
1 mg/day
2 mg/day
4 mg/day

FIG. 3

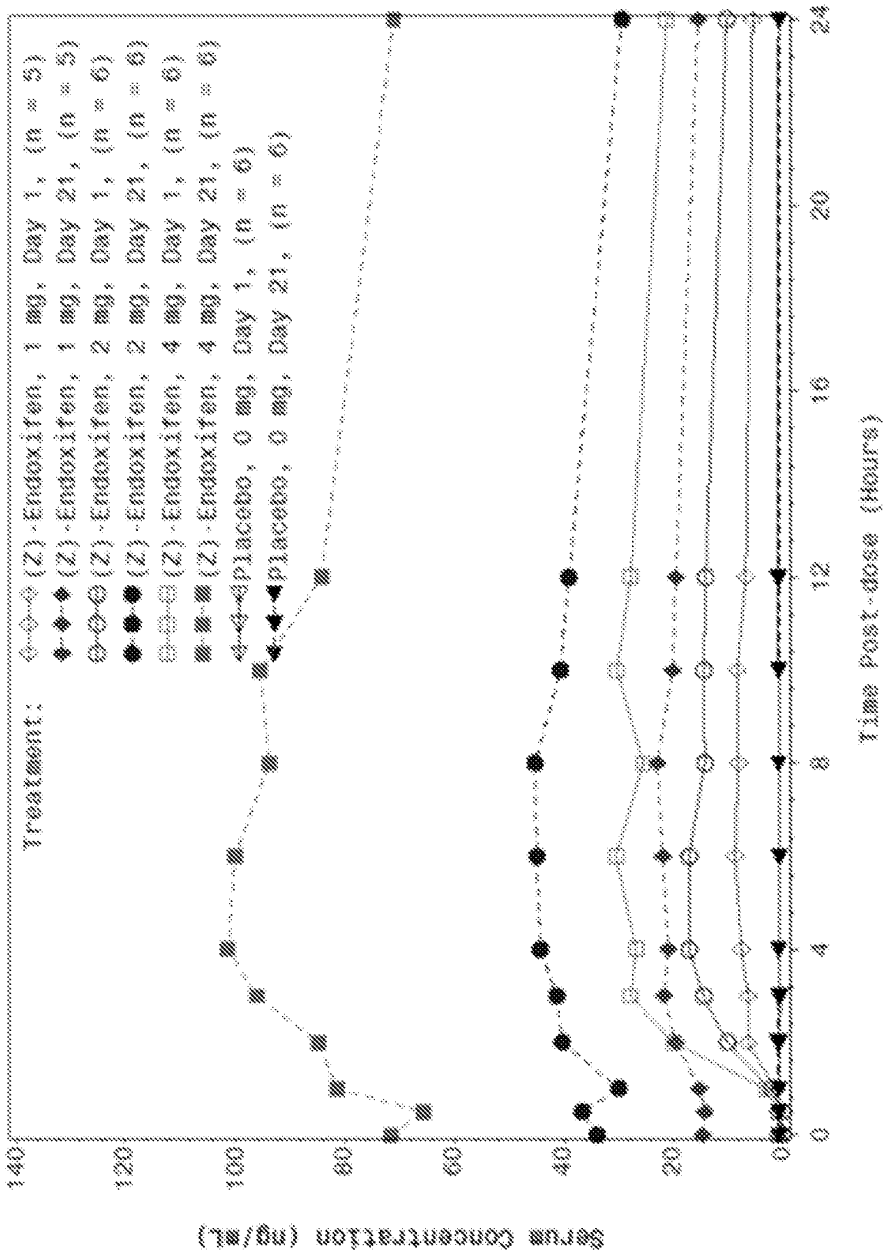

Treatment:
(Z)-Endoxifen, 1 mg, Day 1, (n = 5)
(Z)-Endoxifen, 1 mg, Day 21, (n = 5)
(Z)-Endoxifen, 2 mg, Day 1, (n = 6)
(Z)-Endoxifen, 2 mg, Day 21, (n = 6)
(Z)-Endoxifen, 4 mg, Day 1, (n = 6)
(Z)-Endoxifen, 4 mg, Day 21, (n = 6)
Placebo, 0 mg, Day 1, (n = 6)
Placebo, 0 mg, Day 21, (n = 6)
Serum Concentration (ng/mL)
0
20
40
60
80
100
120
140
0
4
8
12
16
20
24
Time Post-dose (Hours)

FIG. 4

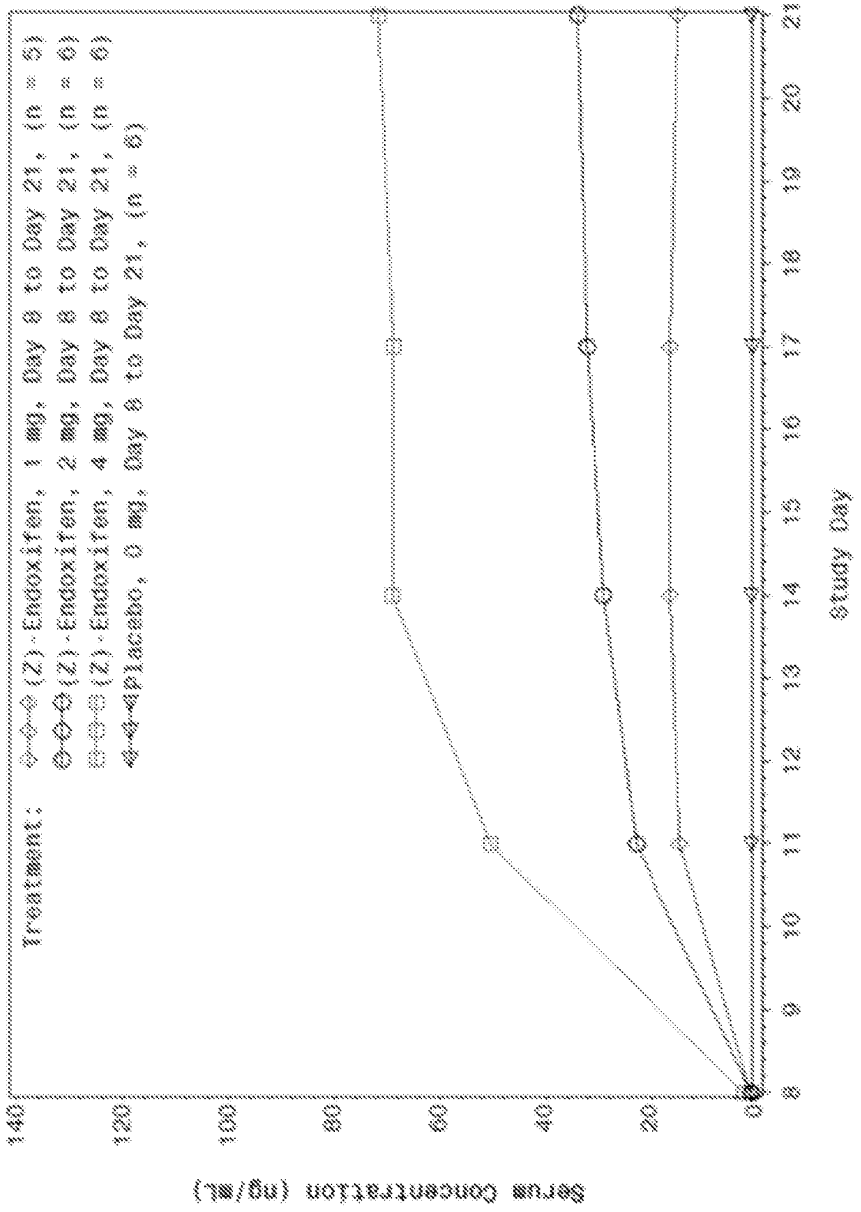

Treatment:
(Z)-Endoxifen, 1 mg, Day 0 to Day 21, (n = 5)
(Z)-Endoxifen, 2 mg, Day 0 to Day 21, (n = 6)
(Z)-Endoxifen, 4 mg, Day 0 to Day 21, (n = 6)
Placebo, 0 mg, Day 0 to Day 21, (n = 6)
Serum Concentration (ng/mL)
0
20
40
60
80
100
120
140
Study Day
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21

FIG. 5

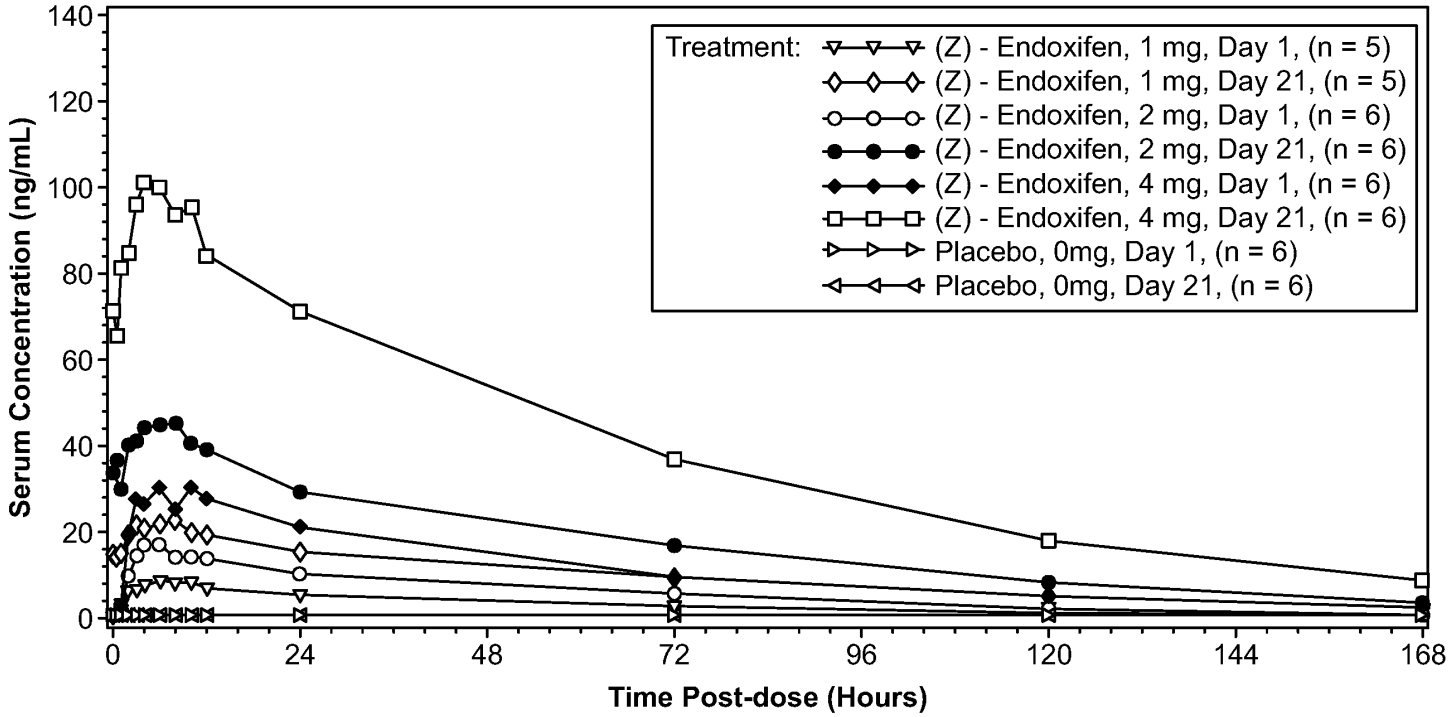

Treatment:
(Z) - Endoxifen, 1 mg, Day 1, (n = 5)
(Z) - Endoxifen, 1 mg, Day 21, (n = 5)
(Z) - Endoxifen, 2 mg, Day 1, (n = 6)
(Z) - Endoxifen, 2 mg, Day 21, (n = 6)
(Z) - Endoxifen, 4 mg, Day 1, (n = 6)
(Z) - Endoxifen, 4 mg, Day 21, (n = 6)
Placebo, 0mg, Day 1, (n = 6)
Placebo, 0mg, Day 21, (n = 6)
Serum Concentration (ng/mL)
0
20
40
60
80
100
120
140
0
24
48
72
96
120
144
168
Time Post-dose (Hours)

FIG. 6

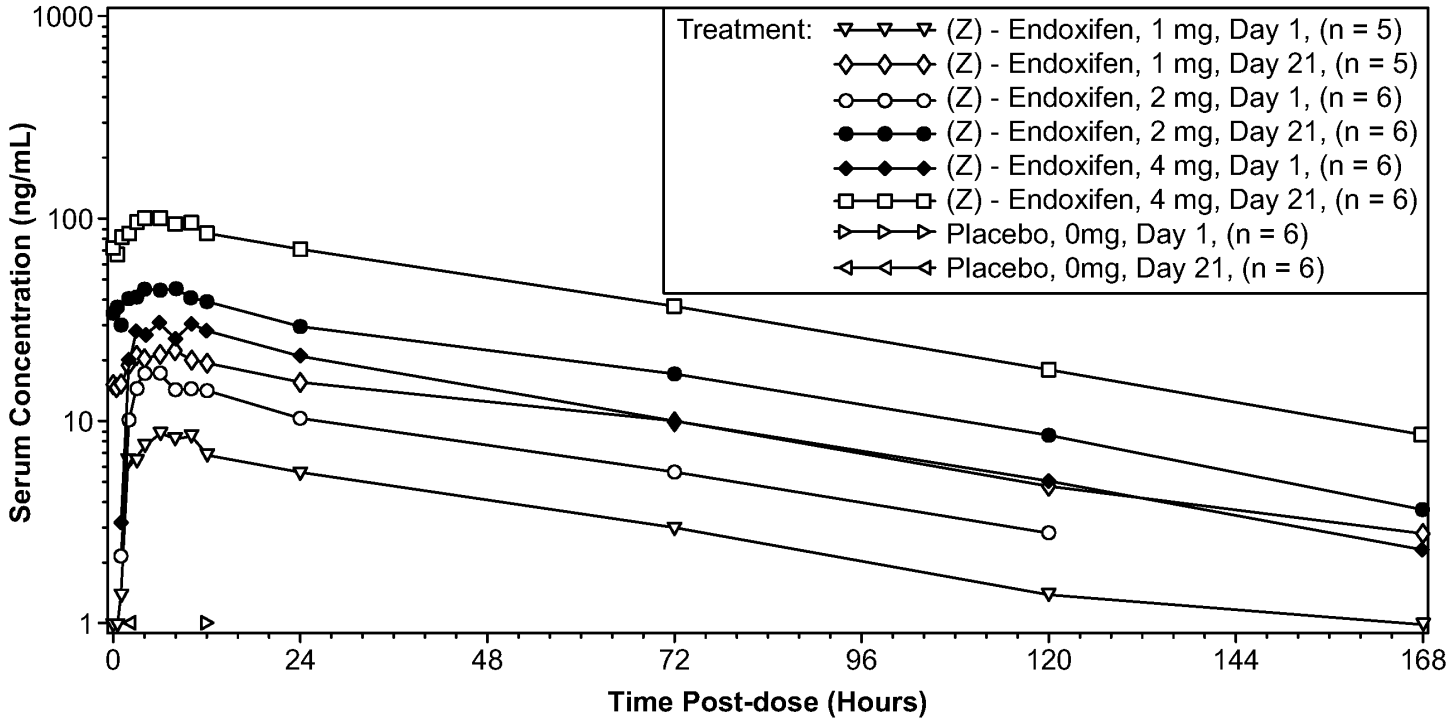

Treatment:
(Z) - Endoxifen, 1 mg, Day 1, (n = 5)
(Z) - Endoxifen, 1 mg, Day 21, (n = 5)
(Z) - Endoxifen, 2 mg, Day 1, (n = 6)
(Z) - Endoxifen, 2 mg, Day 21, (n = 6)
(Z) - Endoxifen, 4 mg, Day 1, (n = 6)
(Z) - Endoxifen, 4 mg, Day 21, (n = 6)
Placebo, 0mg, Day 1, (n = 6)
Placebo, 0mg, Day 21, (n = 6)
Serum Concentration (ng/mL)
1000
100
10
1
0
24
48
72
96
120
144
168
Time Post-dose (Hours)

FIG. 7

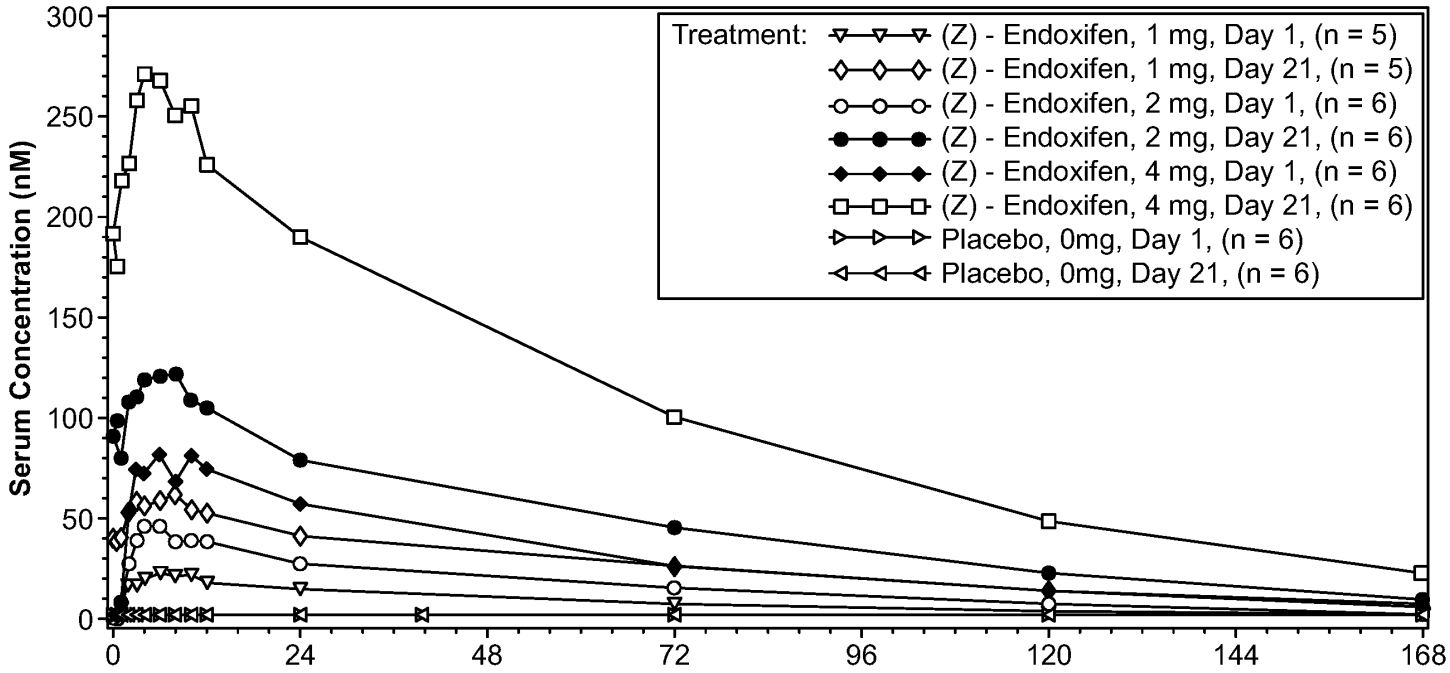


FIG. 8

REPLACEMENT SHEET

8/13

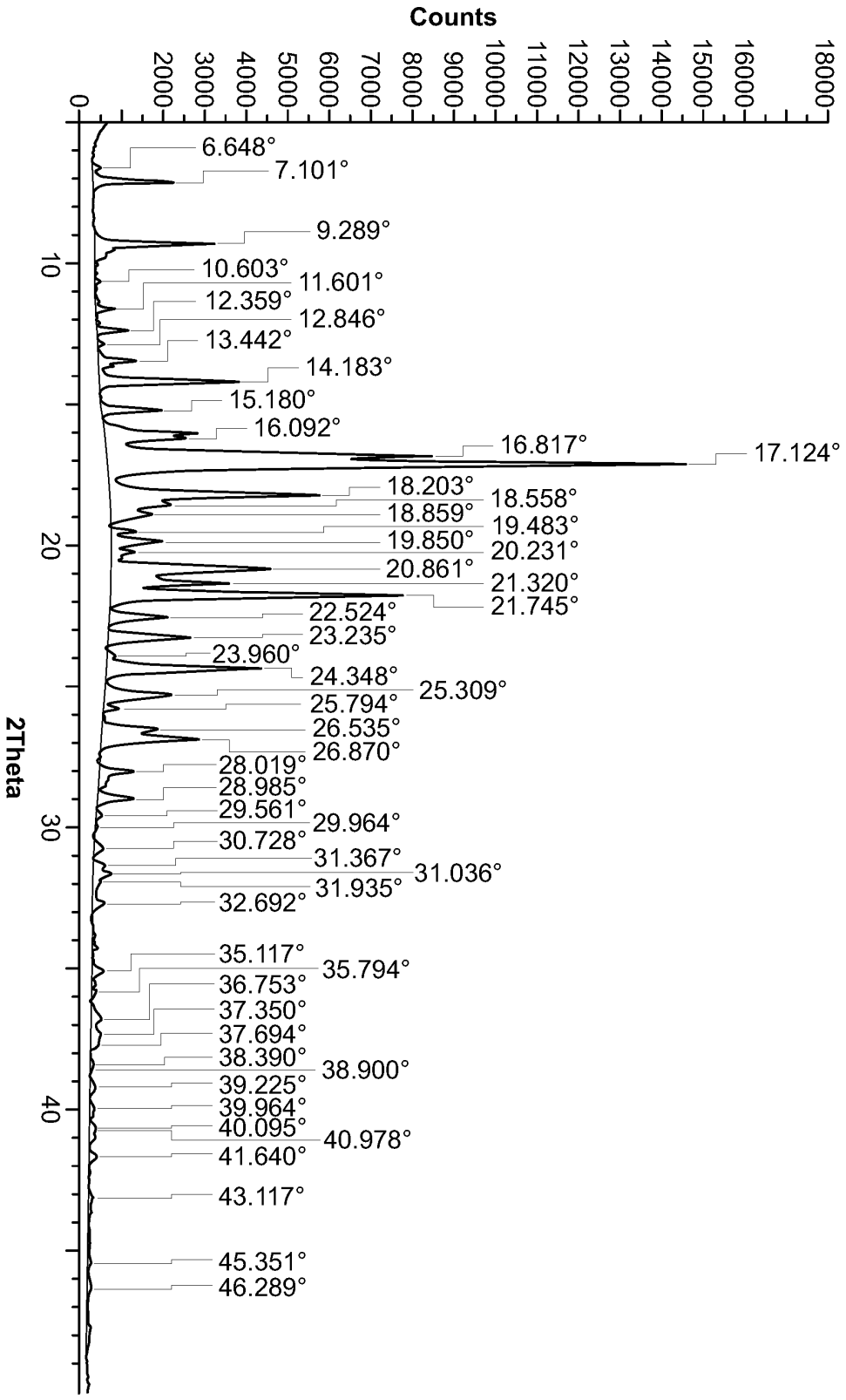


FIG. 9

REPLACEMENT SHEET

FIG. 10

REPLACEMENT SHEET

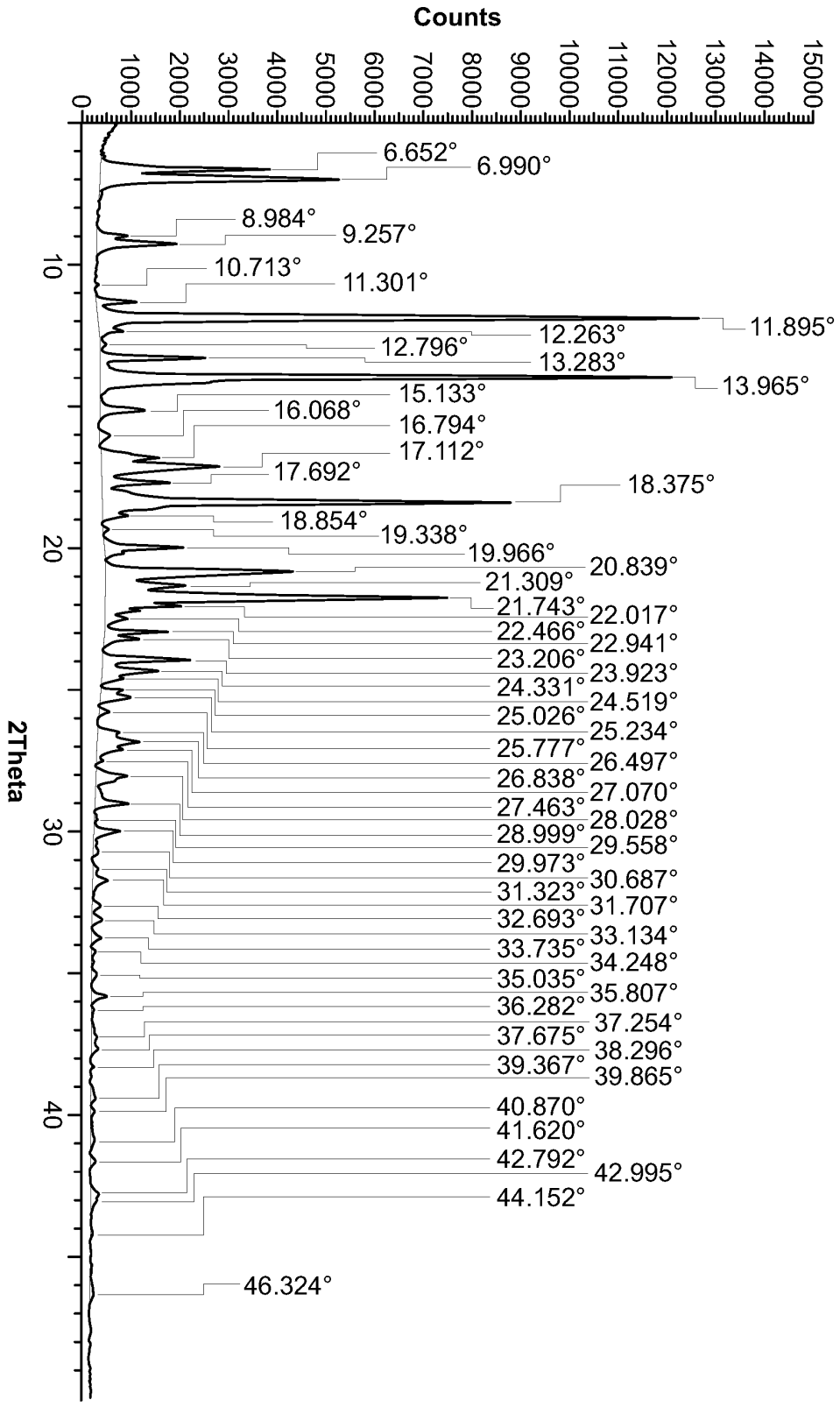


FIG. 11

REPLACEMENT SHEET

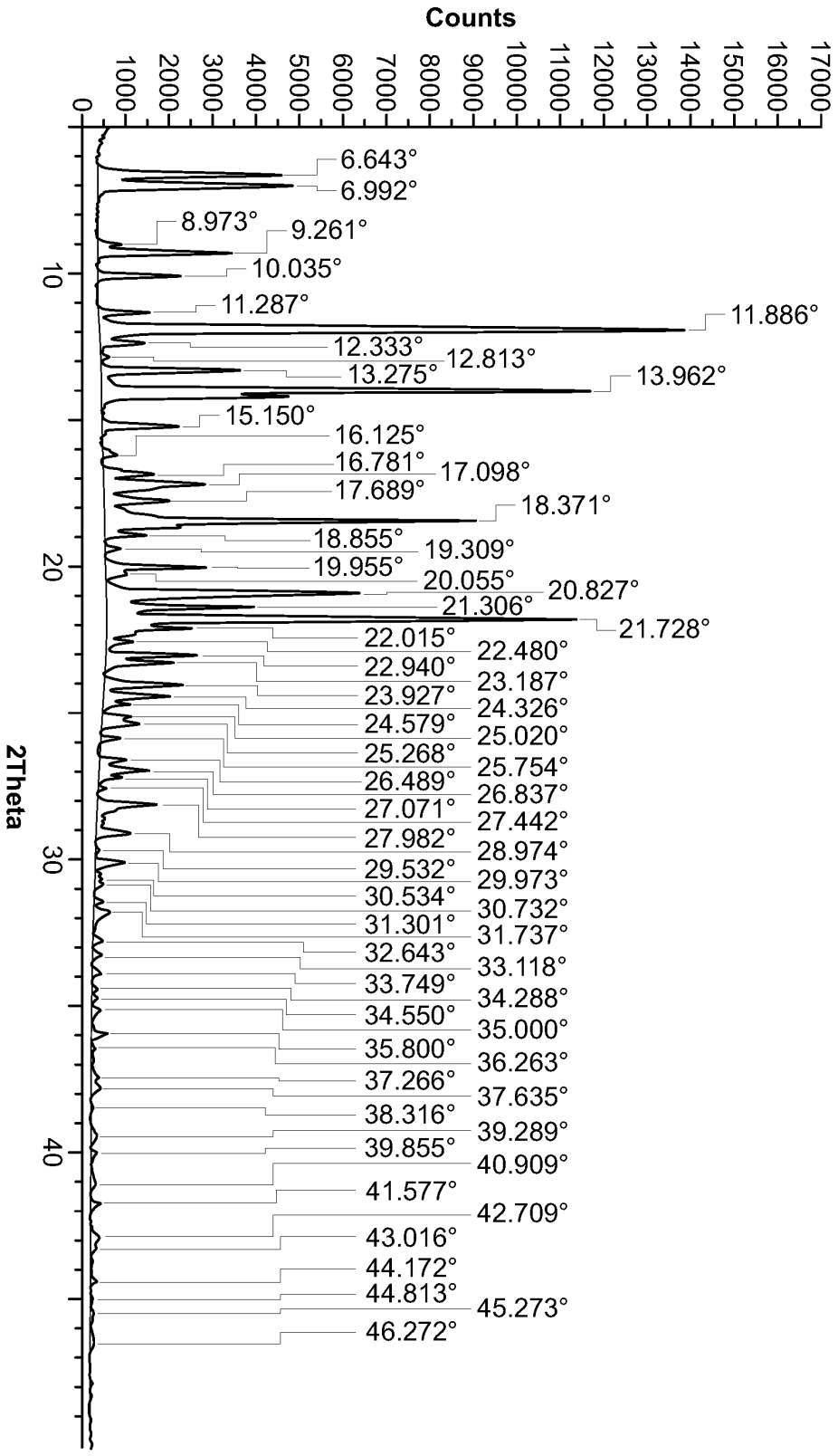


FIG. 12

REPLACEMENT SHEET

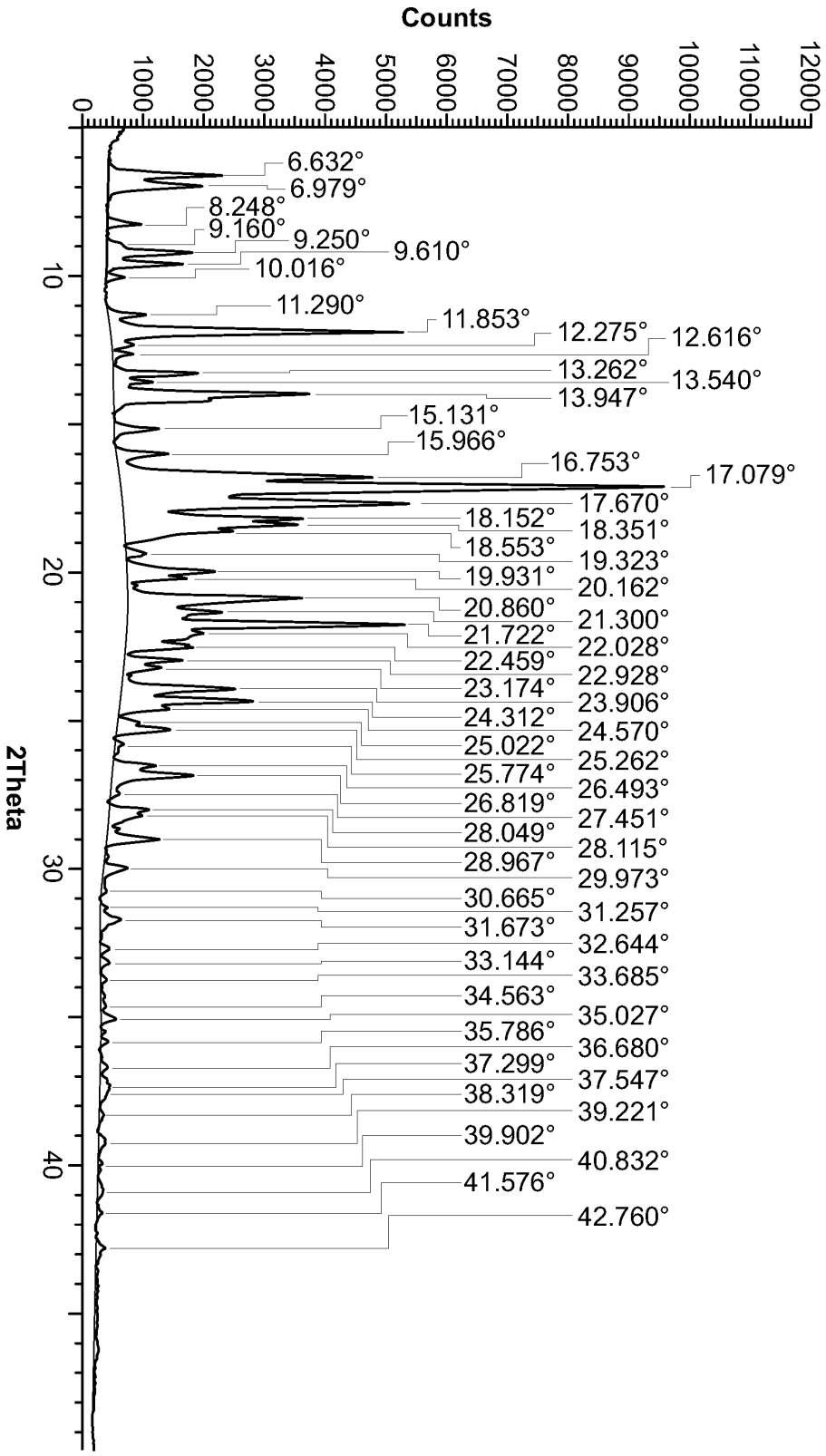


FIG. 13

REPLACEMENT SHEET

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/128,536	03/30/2023	Steven C. Quay	438558-758053	1025

187495 7590 06/10/2024

DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

EXAMINER	
HENLEY III, RAYMOND J	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
06/10/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

seattlepatentdocket@us.dlapiper.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
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Application No. : 18128536
Applicant : Quay
Filing Date : 03/30/2023
Date Mailed : 06/10/2024

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given two (2) months from the mail date of this Notice within which to respond. This time period for reply is extendable under 37 CFR 1.136(a) for only TWO additional MONTHS.

The informalities requiring correction are indicated in the attachment(s). If the informality pertains to the abstract, specification (including claims) or drawings, the informality must be corrected with an amendment in compliance with 37 CFR 1.121 (or, if the application is a reissue application, 37 CFR 1.173). Such an amendment may be filed after payment of the issue fee if limited to correction of informalities noted herein. See Waiver of 37 CFR 1.312 for Documents Required by the Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004). In addition, if the informality is not corrected until after payment of the issue fee, for purposes of 35 U.S.C. 154(b)(1)(iv), "all outstanding requirements" will be considered to have been satisfied when the informality has been corrected. A failure to respond within the above-identified time period will result in the application being ABANDONED.

See attachment(s).

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

/Midel Geronimo/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 18128536 **Drawings filed: 03/30/2023**

IDENTIFICATION OF DRAWING DEFICIENCIES

- [ ] There is a hole or the image thereof within the illustration. FIG(s)
- [ ] The illustration is penetrated or traversed by a solid or broken line that is not intended to be part of the drawing, such as a dark line caused by a flaw in the copying process. FIG(s)
- [ ] An ink stamp or the image thereof obscures part of the illustration. FIG(s)
- [ ] The drawing is marred by black smudges, obliterations, or fax/copier marks (for example, speckles or dots in a substantial portion of the drawing). FIG(s)
- [ ] Figure numbers are duplicated or missing. FIG(s)
- [ ] Drawing sheet or figure is missing. FIG(s)
- [ ] Numbers, letters, or reference characters in the drawing have been crossed out or are illegibly handwritten. FIG(s)
- [X] The character of the lines, numbers, and letters is poor. FIG(s) 2-13
- [ ] The drawing's background shows that the original drawing was made on graph paper or other paper with a pattern or decoration. FIG(s)
- [ ] The FIG. number label is placed in a location that causes the drawing to be read upside down. FIG(s)
- [X] Data, a reference number, or part of the drawing is truncated or missing, or a lead line has no reference number. FIG(s) 2-13
- [ ] The drawing and/or the FIG. label contain(s) foreign language. FIG(s)
- [ ] This utility application contains a photograph of a view that is capable of being illustrated as a line drawing. FIG(s)
- [ ] A petition under 37 CFR 1.84(a)(2) to accept color drawings has been granted, but the brief description of the drawings in the specification does not contain (or has not been amended to contain) the paragraph required by 37 CFR 1.84(a)(2)(iii).
- [ ] This reissue application contains added and/or amended drawings that are not labeled as “New” or “Amended” or “Canceled” as required by 37 CFR 1.173(b)(3). FIG(s)
- [ ] This Design reissue application contains a drawing that is labeled as “Canceled” but is not surrounded by brackets, or a drawing that is surrounded by brackets but is not labeled as “Canceled.” See 37 CFR 1.173(b)(3). FIG(s)
- [ ] OTHER:
- [ ] COMMENTS:

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on June 21, 2024

DLA PIPER LLP (US)

By: /Hillary Pratt/

Attorney Docket No.: 438558-758053

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Confirmation No.: 1025
Steven C. Quay et al.	
Application No.: 18/128,536	Examiner: RAYMOND J HENLEY III
Filed: March 30, 2023	Art Unit: 1629
For: METHODS FOR MAKING AND USING ENDOXIFEN	RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS
Customer No.: 187495	

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

In response to the Notice to File Corrected Application Papers mailed June 10, 2024, please enter the following amendments and remarks.

Amendments to the Drawings are reflected in an attached replacement sheet and are discussed on page 2.

Remarks begin on page 3.

1610972494.2

Intas Exhibit 1002
Page 394 of 408
PGR2025-00043

Amendments to the Drawings:

Please replace original drawing sheets 2–13 respectively, with the attached replacement sheets. The attached replacement sheets have been relabeled in accordance with 37 CFR 1.84(u)(1). Entry is respectfully requested.

Attachment: Replacement Sheets

REMARKS

Applicant submits Replacement Drawing Sheets in response to the Notice to File Corrected Application Papers mailed June 10, 2024. Accordingly, no new matter has been added. Reconsideration is respectfully requested.

Further, the Commissioner is hereby authorized to charge any additional fees or credit any overpayment in connection with this paper to Deposit Account No. 07-1896.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 215-656-3366.

Respectfully submitted,

Dated: June 21, 2024

/Emma K. Holland/

Emma K. Holland, Ph.D.
Registration No. 79,947

DLA PIPER LLP (US)
701 Fifth Avenue, Suite 6900
Seattle, Washington 98104-7029
Tel: (206) 839-4800
Fax (206) 839-4801

1610972494.2

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/128,536	03/30/2023	Steven C. Quay	438558-758053	1025

187495 7590 06/27/2024

DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

EXAMINER	
HENLEY III, RAYMOND J	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
06/27/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

seattlepatentdocket@us.dlapiper.com

Response to Rule 312 Communication	Application No.	Applicant(s)	
	18/128,536	Quay et al.	
	Examiner	Art Unit	AIA (FITF) Status
	RAYMOND J HENLEY III	1629	Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☑ The amendment filed on 29 May 2024 under 37 CFR 1.312 has been considered, and has been:
   a) ☑ entered.
   b) ☐ entered as directed to matters of form not affecting the scope of the invention.
   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
      Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.
   d) ☐ disapproved. See explanation below.
   e) ☐ entered in part. See explanation below.
   f) ☐ not entered because the supplemental or corrected Application Data sheet (ADS)
      ☐ was not accompanied by a petition to accept an unintentionally delayed claim under 37 CFR 1.55 or 27 CFR 1.78;
      ☐ did not identify the information being changed in accordance with 37 CFR 1.76(c)(2);
      ☐ was not properly signed in accordance with 37 CFR 1.76(e) (or 37 CFR 1.33(b) for applications filed prior to September 16, 2012).

/RAYMOND J HENLEY III/
Primary Examiner, Art Unit 1629

OK TO ENTER: /R.J.H/

I hereby certify that this correspondence is being filed via EFS-Web with the United States Patent and Trademark Office on May 29, 2024.

DLA PIPER LLP (US)

By: /Hillary Pratt/

Attorney Docket No.: 438558-758053

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Steven C. Quay et al. Application No.: 18/128,536 Filed: March 30, 2023 For: METHODS FOR MAKING AND USING ENDOXIFEN Customer No. 187495	Confirmation No. 1025 Examiner: RAYMOND J HENLEY III Art Unit: 1629 **AMENDMENT AFTER ALLOWANCE UNDER 37 C.F.R. § 1.312**

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Prior to issuance of the patent, Applicant respectfully requests entry of this amendment under 37 C.F.R. § 1.312 for the above-captioned patent application.

Amendments to the Specification begin on page 2.

Amendments to the Claims are reflected in the listing of claims beginning on page 3.

Remarks begin on page 9.

1609811691.1

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PATENT AND TRADEMARK OFFICE

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ELECTRONIC PAYMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/128,536	07/19/2024 07:53:40 PM Z ET	438558-758053

Title of Invention

METHODS FOR MAKING AND USING ENDOXIFEN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1025	FILED BY	Hillary Pratt
PATENT CENTER #	66445801	AUTHORIZED BY	Emma Holland
CUSTOMER #	187495	FILING DATE	03/30/2023
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Steven C. Quay

Payment Information

PAYMENT METHOD	PAYMENT TRANSACTION ID	PAYMENT AUTHORIZED BY
DA / 071896	E20247J54155206	Hillary Pratt

PRE-AUTHORIZED ACCOUNT	PRE-AUTHORIZED CATEGORY
071896	37 CFR 1.16 (National application filing, search, and examination fees); 37 CFR 1.17 (Patent application and reexamination processing fees); 37 CFR 1.19 (Document supply fees); 37 CFR 1.20 (Post Issuance fees); 37 CFR 1.21 (Miscellaneous fees and charges)

FEE CODE	DESCRIPTION	ITEM PRICE($)	QUANTITY	ITEM TOTAL($)
2501	UTILITY ISSUE FEE	480.00	1	480.00
			TOTAL AMOUNT:	$480.00

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement

Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #	RECEIPT DATE / TIME	ATTORNEY DOCKET #
18/128,536	**07/19/2024 07:53:40 PM Z ET**	**438558-758053**

Title of Invention

METHODS FOR MAKING AND USING ENDOXIFEN

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	-
CONFIRMATION #	1025	FILED BY	Hillary Pratt
PATENT CENTER #	66445801	FILING DATE	03/30/2023
CUSTOMER #	187495	FIRST NAMED INVENTOR	Steven C. Quay
CORRESPONDENCE ADDRESS	-	AUTHORIZED BY	Emma Holland

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
438558-758053_Issue_Fee_Transmittal.pdf	1	Issue Fee Payment (PTO-85B)	198 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
438558-758053_Issue_Fee_Transmittal.pdf	C68CEDF6286069F00BFACDC4DA3849C59E4031AC24E4BF8741D5F38E5447AD79F4781698C2C31F92CE1D3DDE2B431B512C1FEF632354063F982FA1A2E6AD9FD2

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via the USPTO patent electronic filing system.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications. **Because electronic patent issuance may occur shortly after issue fee payment, any desired continuing application should preferably be filed prior to payment of this issue fee in order not to jeopardize copendency.**

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

187495 7590 05/03/2024

DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via the USPTO patent electronic filing system or by facsimile to (571) 273-2885, on the date below.

Hillary Pratt	(Typed or printed name)
/Hillary Pratt/	(Signature)
July 19, 2024	(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/128,536	03/30/2023	Steven C. Quay	438558-758053	1025

TITLE OF INVENTION: METHODS FOR MAKING AND USING ENDOXIFEN

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$480	$0.00	$0.00	$480	08/05/2024

EXAMINER	ART UNIT	CLASS-SUBCLASS
HENLEY III, RAYMOND J	1629	514-651000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/AIA/122 or PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/AIA/47 or PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 DLA Piper LLP
2 Melissa M. Harwood, Ph.D.
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: ATOSSA THERAPEUTICS, INC.

(B) RESIDENCE: (CITY and STATE OR COUNTRY): SEATTLE, WA

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☒ Issue Fee ☐ Publication Fee (if required)

4b. Method of Payment: *(Please first reapply any previously paid fee shown above)*

☒ Electronic Payment via the USPTO patent electronic filing system ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. 07-1896

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

☐ Applicant asserting small entity status. See 37 CFR 1.27

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

☐ Applicant changing to regular undiscounted fee status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature /Emma K. Holland/ Date July 19, 2024

Typed or printed name Emma K. Holland, Ph.D. Registration No. 79,947

PTOL-85 Part B (11/23) Approved for use through 03/31/2026 OMB 0651-0033 U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Intas Exhibit 1002
Page 404 of 408
PGR2025-00043

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APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/128,536	08/27/2024	12071391	438558-758053	1025

187495 7590 08/07/2024

DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

ISSUE NOTIFICATION

The projected patent number and issue date are specified above. The patent will issue electronically. The electronically issued patent is the official patent grant pursuant to 35 U.S.C. § 153. The patent may be accessed on or after the issue date through Patent Center at https://patentcenter.uspto.gov/. The patent will be available in both the public and the private sides of Patent Center. Further assistance in electronically accessing the patent, or about Patent Center, is available by calling the Patent Electronic Business Center at 1-888-217-9197.

The USPTO is implementing electronic patent issuance with a transition period, during which period the USPTO will mail a ceremonial paper copy of the electronic patent grant to the correspondence address of record. Additional copies of the patent (i.e., certified and presentation copies) may be ordered for a fee from the USPTO's Certified Copy Center at https://certifiedcopycenter.uspto.gov/index.html. The Certified Copy Center may be reached at (800)972-6382.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Center (https://patentcenter.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Patents Stakeholder Experience (OPSE), Stakeholder Support Division (SSD) at (571)-272-4200.

INVENTOR(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional inventors):

Steven C. Quay, Seattle, WA;
Yao-Lin Sun, Tainan City, TAIWAN;
LungHu Wang, Kaohsiung City, TAIWAN;
ChangJung Wu, Kaohsiung City, TAIWAN;
ChuanDer Huang, Tainan City, TAIWAN;

APPLICANT(s) (Please see PATENT CENTER site https://patentcenter.uspto.gov for additional applicants):

Atossa Therapeutics, Inc., Seattle, WA;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
18/128,536	03/30/2023	Steven C. Quay	438558-758053	1025

187495 7590 08/27/2024

DLA Piper LLP
701 Fifth Avenue
Suite 6900
Seattle, WA 98104

EXAMINER	
HENLEY III, RAYMOND J	

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
08/27/2024	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

seattlepatentdocket@us.dlapiper.com

APPLICATION NO.	ISSUE DATE	PATENT NO.
18/128,536	27-Aug-2024	12071391

DLA Piper LLP
701 Fifth Avenue
Seattle, WA 98104

EGRANT NOTIFICATION

Your electronic patent grant (eGrant) is now available, which can be accessed via Patent Center at https://patentcenter.uspto.gov

The electronic patent grant is the official patent grant under 35 U.S.C. 153. For more information, please visit https://www.uspto.gov/electronicgrants